

Late eczematous reactions to food in children with atopic dermatitis

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Summary

Background Food allergy is a common problem in patients with atopic dermatitis (AD), particularly in children. While immediate reactions to food are well characterized, the importance of food as a provocation factor for late eczematous reactions has been a subject of debate for several decades.

Objective To investigate the importance of food for the induction of late eczematous reactions in children with AD and to correlate the clinical outcome to the results of specific IgE determinations and atopy patch tests (APT).

Methods One hundred and six double-blind placebo-controlled food challenges (DBPCFCs) to cow's milk, hen's egg, wheat and soy in 64 children with AD (median age 2 years) were analysed retrospectively. Total and food-specific IgE were determined by CAP RAST FEIA and APTs with native foodstuff were performed. The diagnostic values of specific IgE and APT results were calculated.

Results Forty-nine (46%) of the challenges were related to a clinical reaction. An exacerbation of AD (late eczematous reaction) commonly occurred 24 h after the ingestion of food. Isolated late eczematous reactions were seen in 12% of all positive challenges. Forty-five percent of the positive challenges were associated with late eczematous responses, which followed immediate-type reactions. The sensitivity of food-specific IgE and the APT was 76% and 70%, respectively. Specific IgE and APT were often false positive, which resulted in low positive predictive values (64% and 45%, respectively).

Conclusions Late eczematous reactions may often be observed upon food challenge in children with AD. Due to the poor reliability of food-specific IgE and APT results DBPCFCs have still to be regarded as the gold standard for the appropriate diagnosis of food responsive eczema in children with AD.

Keywords atopic dermatitis, atopy patch test, food allergy, food challenge, food responsive eczema, food-specific IgE

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease, which commonly begins in early infancy, runs a course of exacerbations and remissions and is associated with a characteristic distribution and morphology of skin lesions. Furthermore, pruritus and subsequently sleeplessness are hallmarks of AD [1]. Numerous trigger factors have been identified for AD over the last decades, such as inhalative allergens, food allergens, irritative substances and infectious microorganisms like *Staphylococcus aureus* and *Malassezia furfur* [2–4]. There is substantial evidence that foods like cow's milk and hen's egg are major provocation factors for the flares of AD in infancy, while inhalant allergens and pollen-related foods are of greater importance in adults [5–9].

According to Wüthrich, three patterns of cutaneous reactions to food may occur in patients with AD upon oral challenge [10]:

- (i) Immediate-type reactions such as urticaria, angioedema and erythema, commonly occurring a few minutes after ingestion of food without an exacerbation of AD. Additionally, gastrointestinal, respiratory and cardiovascular symptoms may evolve.
- (ii) Pruritus occurring soon after the ingestion of food with subsequent scratching leading to an exacerbation of AD.
- (iii) Exacerbations of AD occurring after 6–48 h termed late reactions. Late reactions may occur also after an immediate-type response.

The prevalence of food allergy in infants with AD was reported in a range between 20% and 80% in various studies, and may be estimated at 30% [11–13]. Hen's egg, cow's milk, soy and wheat account for about 90% of allergenic foods in children with AD [11, 14]. Dependent on the kind of food,

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most of the children may outgrow their food allergy [15]. Immediate-type responses to these foods are well characterized in children with AD, but there are only few trials studying true late eczematous responses, which need 6–48 h to develop and may occur only after repetitive ingestion of food.

Reliable markers for the identification of patients with food responsive eczema are still lacking. Anamnestic data given by the parents often do not correlate with the findings of an oral challenge, particularly with regard to eczematous reactions [7, 9, 16, 17]. Moreover, only 25–30% of all patients with food-specific IgE have been shown to react to the respective food in oral provocation tests [18]. Due to the limited reliability of the personal history and of food-specific IgE, double-blind placebo-controlled food challenges (DBPCFCs) have been regarded as the gold standard for the diagnosis of food allergy-related diseases since 1976 [19]. Over the last years, the atopy patch test (APT) has become a popular diagnostic tool for the identification of food allergy in patients with AD, but the predictive accuracy remains controversial in different studies [20–22].

In order to investigate the importance of food for the induction of allergic reactions in children with AD we analysed the results of 106 DBPCFC retrospectively. Furthermore, the clinical outcome was correlated to the results of specific IgE determinations and APT.

Materials and methods

Patients

The results of 106 DBPCFC were analysed retrospectively. The food challenges were performed in 64 children aged 1–10 years (median 2 years) with mild-to-severe AD who visited the Department of Dermatology and Allergology of the Hannover Medical University as outpatients. AD was diagnosed following the criteria of Hanifin and Rajka, which include pruritus, a typical morphology and distribution of eczematous lesions, chronicity of the disease and a personal or family history of atopy [23]. A detailed medical history was obtained. Severity of AD was determined according to the SCORAD, which is a scoring system combining extent, severity and subjective symptoms [24]. The maximum possible score is 103 points. The inclusion criteria were suspicion of food-related worsening of AD or immediate-type reactions by parents and/or referring doctor. Informed consent was obtained for the DBPCFC. The oral challenge test was approved by the ethics committee of the institution.

Specific IgE

Total IgE and specific IgE to food (cow's milk, hen's egg, wheat, soy) were determined in all 64 children using the CAP RAST FEIA according to the manufacturer's instructions (Pharmacia Freiburg, Germany) prior to the DBPCFC. The detection limit was 0.35 kU/L. If specific IgE was above the detection limit, the children were regarded as sensitized.

APT

APTs with fresh pasteurized cow's milk containing 3.5% fat, hen's egg powder (Behr, Hamburg, Germany), wheat gluten

(Kröner GmbH, Ibbenbüren, Germany) and soy milk (Vitaquell, Hamburg, Germany) were performed in 41 children who had no eczematous lesions on their back. The food was applied on unaffected back skin under 12 mm aluminium chambers (Finn Chambers on Scanpor, Hermal, Reinbek, Germany). A paste was prepared using hen's egg powder/wheat gluten and a 0.9% sodium chloride solution. About 20 mg of hen's egg paste, wheat paste, 25 µL of cow's milk, 25 µL soy milk were placed on filter paper and occluded for 24 h. The test was read 30 min after removal of the Finn Chambers and 24 and 48 h thereafter. The test sites were considered as positive, if an erythema together with an infiltration had occurred. Erythema without infiltration was regarded as an irritative reaction.

DBPCFC

The suspected foods were avoided for 4 weeks prior to DBPCFC upon instruction by a dietitian. Local therapy with mild corticosteroids and emollients remained stable during the challenge. Antihistamines were withdrawn at least 72 h prior to the challenge. Verum and placebo were given to each patient on 2 consecutive days in random order, with a free interval of 1 day between placebo and verum challenge. The sequence of challenges was determined by the dietitian. A verum:placebo ratio of 2:1 was used. The amount of challenged food was adapted to a normal daily intake. In general, full doses amounted to 150 mL of fresh pasteurized cow's milk, 10 g of hen's egg powder, equivalent to one egg (Behr, Hamburg, Germany), 5 g of wheat gluten, equivalent to one slice of wheat bread (Kröner GmbH, Ibbenbüren, Germany) or 150 mL of soy milk (Vitaquell, Hamburg, Germany). In order to blind the food challenge, the full doses of cow's milk, hen's egg, wheat gluten and soy milk were mixed with 150 mL extensively hydrolysed soy formula (Pregomin, Milupa, Germany) and black currant flavour (SHS, Gesellschaft für klinische Ernährung, Heilbronn, Germany). Soy hydrolysate mixed with black currant flavour was used as placebo and was given in equal volume as the verum. Seven successive doses of food were given on the first day of the verum/placebo challenges until the full dose was ingested or a reaction occurred. The doses of verum/placebo mixture were as follows: 0.2 mL (i.e. 0.1 mL of cow's milk), 0.6, 2.0, 6.0, 20.0, 60.0 and 200.0 mL. The interval between the doses was 30 min. On the second day, the full dose was given all at once. The children were observed for 48 h after the placebo/verum challenge. All reactions were recorded. The severity of AD was assessed daily prior to challenge according to the SCORAD by a physician unaware of the given food. A reaction was considered as immediate if occurring within 6 h upon ingestion of the last dose, thereafter as late reaction. In case of an immediate reaction that was more severe than a localized urticaria or erythema (i.e. angioedema, generalized urticaria/erythema, nausea, vomiting, rhinitis or bronchial obstruction) oral antihistamines and rectal corticosteroids were administered. An increase of 10 SCORAD points or more was considered as a significant deterioration of eczema (late eczematous reaction).

In total, 106 verum challenges and 52 placebo challenges were performed in 64 children. Thirty-three children were challenged with one food, 21 children with two, nine children

with three, and only one child with all four foods (mean number of provocations per child 1.6).

Statistical analysis

The comparison of the medians of non-parametric data of the patient groups was performed with the Mann–Whitney rank sum test. Mean values of parametric data were compared with Student's *t*-test. The difference of the SCORAD before and after challenge was calculated with the paired *t*-test. The differences in the distribution of a condition or trait between two groups was calculated with the Fisher Exact test which computes the exact two-tailed probabilities of observing a specific 2 × 2 contingency table.

Two-by-two tables were used to calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for personal history, food-specific IgE and APT. Combined reactions were analysed as both immediate reactions and late reactions. The sensitivity is defined as the proportion of true positive test results among the patients with a positive challenge tests (the power of the test method to identify symptomatic individuals), the specificity as the proportion of true negative test results among the patients with a negative challenge test (the power of the test method to identify asymptomatic individuals). PPV is defined as the proportion of patients reacting to a challenge test among the patients with a positive test result (the power of the test to predict food allergy) and NPV is defined as the proportion of non-reacting patients among the patients with a negative test results (the power of the test to predict the absence of food allergy).

Results

Clinical outcome of oral challenge tests

One hundred and six food challenge tests with cow's milk, hen's egg, wheat gluten or soy milk were performed in 64 children with AD. Forty-one (64%) of the children showed a reaction to at least one kind of food. Thirty-four (83%) of these children reacted to one kind of food, six (15%) children showed a positive reaction to two nutrients and only one child (2%) reacted to three nutrients.

In total 49 (46%) out of 106 of the verum challenges resulted in an allergic reaction, with provocations to hen's egg showing the highest proportion of positive results (see Table 1). Isolated immediate reactions accounted for 21 (43%) out of 49 positive reactions. Six (12%) reactions were isolated late eczematous reactions, all observed after 24 h. In 22 (45%) of the positive reactions immediate symptoms were followed by a late eczematous reaction. The highest percentage of isolated eczematous reactions was observed after challenge with wheat (33%). The individual results of the challenges with cow's milk, hen's egg, wheat and soy are presented in Table 1. Also small doses of food led to allergic reactions in some children (Table 2).

Only two placebo reactions were observed, which points to the validity of the challenge results. These reactions occurred in two children and manifested as pruritus occurring within 2 h. In these children the whole challenge procedure was

Table 1. Proportion of positive clinical reactions upon DBPCFC

Allergen	<i>n</i>	Positive reactions	Immediate	Late phase	Combined
Cow's milk	32	15 (47%)	6 (40%)	2 (13%)	7 (47%)
Hen's egg	31	19 (62%)	10 (53%)	1 (5%)	8 (42%)
Wheat	26	9 (35%)	2 (22%)	3 (33%)	4 (44%)
Soy	17	6 (35%)	3 (50%)	0 (0%)	3 (50%)
All	106	49 (46%)	21 (43%)	6 (12%)	22 (45%)

One hundred and six DBPCFC with cow's milk, hen's egg, wheat and soy were performed in 64 children with AD. DBPCFC, double-blind placebo-controlled food challenge; AD, atopic dermatitis.

repeated. Because no placebo reaction was observable during the second run and clear clinical reactions occurred upon provocation with verum, these results were included into the analysis.

There were no significant differences in terms of age, severity of AD (SCORAD), total IgE and the prevalence of respiratory atopic diseases between the children who reacted to food and those who did not. However, children with a positive reaction had significantly higher levels of the respective specific IgE than those who did not react (median values 1.82 and 0.0 kU/L, respectively, $P < 0.001$).

Immediate reactions

Forty-three (88%) out of the 49 positive reactions resulted in immediate reactions (isolated/combined with late eczematous reactions). No severe anaphylactic reactions were observed. Immediate reactions presented with urticaria ($n = 22$), angioedema ($n = 1$), erythema ($n = 31$), nausea/vomiting ($n = 5$), bronchial obstruction ($n = 1$) or rhinitis ($n = 1$). Skin reactions were always part of the immediate reactions and were the only symptom in 37 (86%) of the immediate reactions. In five (12%), also gastrointestinal symptoms (nausea/vomiting) emerged, and one (2%) immediate reaction was accompanied by respiratory symptoms (rhinitis and bronchial obstruction). These gastrointestinal and respiratory symptoms occurred preferably upon challenge with hen's egg and cow's milk. The highest proportion of reactions involving more than one organ system was seen after provocation with hen's egg. Reactions to wheat and soy were associated with cutaneous symptoms only (Table 3).

Seven (16%) out of the 43 immediate-type reactions occurred after 2–6 h and were therefore termed as delayed immediate-type responses. This pattern was not specific for a certain allergen and manifested as urticaria or erythema. Five

Table 2. Number of children reacting to increasing doses of food

Dose (mL)	Reacting children (<i>n</i>)
0.2	3
0.6	3
2.0	7
6.0	7
20.0	4
60.0	1
200.0	16
300.0 (second day)	8

Table 3. Involved organ systems in immediate (isolated/combined) reactions to individual foods

Allergen	Immediate reactions (n)	Skin	Skin + respiratory tract	Skin + gastrointestinal tract
Cow's milk	13	11 (85%)	2 (15%)	0 (0%)
Hen's egg	18	14 (78%)	3 (17%)	1 (5%)
Wheat	6	6 (100%)	0 (0%)	0 (0%)
Soy	6	6 (100%)	0 (0%)	0 (0%)
All	43	37 (86%)	5 (12%)	1 (2%)

patients additionally developed an exacerbation of eczema as a late reaction. Only one of these patients had been suspected to be allergic to food by the history prior to the challenge.

Interestingly, eight (19%) of the immediate reactions occurred during the second challenge day, after the highest dose had been tolerated on the first day. Five of these reactions were observed upon provocation with cow's milk. They consisted of urticaria, erythema or vomiting. Two patients additionally developed a late reaction as an exacerbation of their eczema 24 h after the challenge.

Late eczematous reactions

Twenty-eight (57%) of the 49 positive reactions resulted in late eczematous reactions (either isolated or in combination with immediate reactions). All late reactions appeared after a period of 24 h following the first food intake. In most cases a deterioration of the eczema presented as a flare up of pre-existing lesions. No late gastrointestinal or respiratory reactions were observed.

In the late reactions, the SCORAD rose on average by 14.2 points after challenge as compared with the baseline value prior to the challenge (mean SCORAD 27.5 and 42.0, respectively, $P < 0.001$). Six isolated eczematous reactions occurred (mean SCORAD before and after challenge 29.7 and 48.3, respectively, $P = 0.02$). Three out of six reactions occurred after challenge with wheat. A deterioration of eczema after ingestion of food had been suspected by the parents in only 33% of these patients. Patients showing an isolated eczematous reaction were significantly older when compared with children showing a combined/immediate reaction (median 3.5 and 1 years, respectively, $P = 0.009$).

Diagnostic accuracy of personal history, food-specific IgE, APT

Personal history The sensitivity of the history was only 34% for immediate reactions and 25% for late eczematous reactions. The sensitivity of the history was highest for cow's

milk (50%/67% for immediate/eczematous reactions), and lowest for soy (0% for immediate and eczematous reactions).

Specificity was 97% for immediate reactions and 85% for eczematous reactions. Specificity was highest for soy (100% for immediate and eczematous reactions) and lowest for cow's milk (95% and 74%). The PPV was 85% for immediate reactions and 33% for eczematous reactions. The PPV was highest for hen's egg (89% and 33%). The NPV was 74% for immediate reactions and 79% for eczematous reactions and was highest for cow's milk (86% and 90%).

Food-specific IgE Food-specific IgE to the respective food was measured in all children by means of CAP RAST FEIA. In general, sensitivity, specificity and PPV were higher for immediate reactions than for eczematous reactions (Table 4). In 67% of the late eczematous reactions food-specific IgE was detected. Analysing early and eczematous reactions together, sensitivities were higher for hen's egg (84%) and cow's milk (73%) than for wheat and soy (each 67%). Specificity was highest for wheat (82%) and lowest for cow's milk (47%). The PPV was 33% for eczematous reactions and 57% for immediate reactions. PPV for single allergens are shown in Fig. 1a. Diagnostic accuracy tended to be higher in children younger than 2 years when compared with older children (see Table 5). There was no correlation between the level of food-specific IgE and the challenge dose, which resulted in an allergic reaction.

In 48 out of 106 DBPCFC no specific IgE to the respective allergen was detected. Twelve (25%) of these challenges resulted in a clinical reaction. Seven (58%) reactions were combined (immediate and eczematous). Three (25%) isolated immediate reactions and two (17%) isolated eczematous reactions occurred. Thus the proportion of DBPCFC leading to eczematous reactions was higher in children who showed no detectable specific IgE to the corresponding food as compared with all positive oral challenges.

There was no significant difference in age, severity of AD and presence of respiratory atopic diseases when children with a positive challenge test and positive food-specific IgE

Table 4. Diagnostic accuracy of specific IgE/APT for immediate/late eczematous reactions

	Any reaction (n = 49)		Immediate reactions (n = 43)		Eczematous reactions (n = 28)	
	Specific IgE (%)	APT (%)	Specific IgE (%)	APT (%)	Specific IgE (%)	APT (%)
Sensitivity	76	70	77	67	68	67
Specificity	63	41	60	38	50	38
PPV	64	45	57	38	33	24
NPV	75	67	79	67	81	79

APT, atopy patch test; PPV, positive predictive value; NPV, negative predictive value.

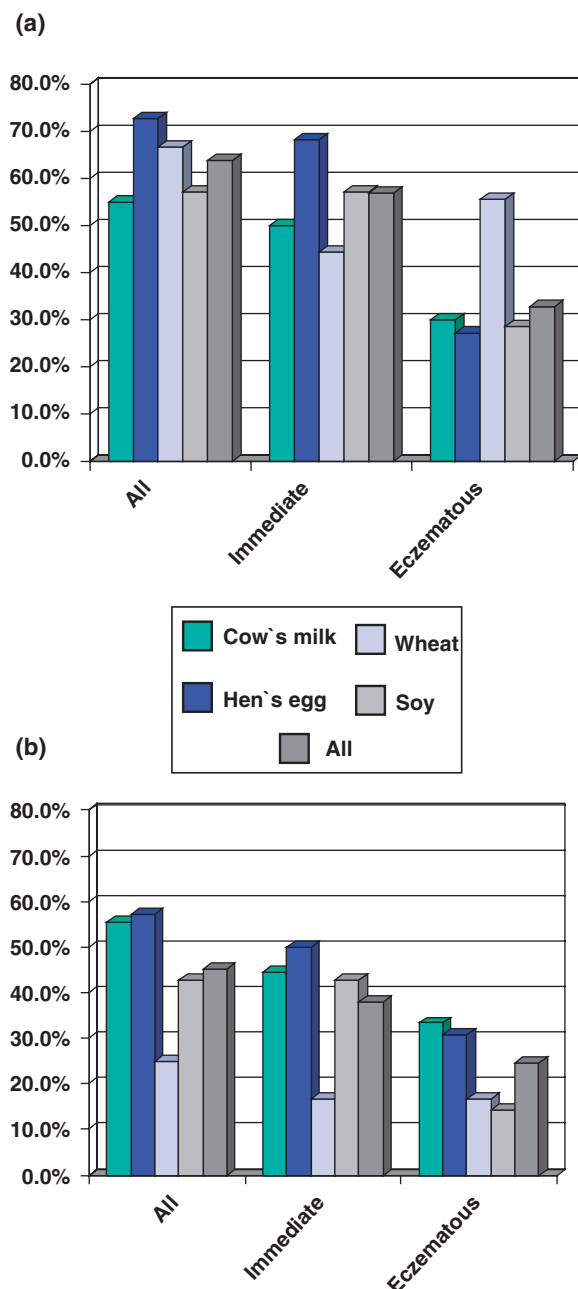


Fig. 1. Positive predictive values (PPV) of specific IgE (a) and APT (b) for single allergens.

were compared with children with a positive challenge who had no food-specific IgE. Total IgE tended to be lower in children without food-specific IgE (45.2 and 215.5 kU/L, respectively, $P = 0.064$). APT was performed in five children with a positive oral challenge and no food-specific IgE. Interestingly, all children showed a positive APT to the respective allergen.

APT APT was performed in 41 out of 64 children. The remaining 23 children had either eczematous lesions on their back or the parents had refused the APT. In total, the outcome of 66 food challenges could be correlated to an APT. Forty-two of 66 APT (63%) resulted in a cutaneous reaction.

Table 5. Diagnostic accuracy of food specific IgE for children younger/older than 2 years

	<2 years (%)	≥2 years (%)
Sensitivity	86	70
Specificity	74	57
PPV	75	56
NPV	95	71

PPV, positive predictive value; NPV, negative predictive value.

In 75% of the late eczematous reactions the APT was also positive. Sensitivity was 67% for immediate and eczematous reactions (Table 4); it was highest for cow's milk (83%) and lowest for wheat (60%). Specificity was 38% for immediate and eczematous reactions; it was highest for soy (60%) and lowest for hen's egg (14%). The PPV was 38% for immediate and 24% for eczematous reactions. The PPV for single foods are presented in Fig. 1b. The NPV was 67% for immediate reactions and 79% for eczematous reactions. The combination of the APT with food-specific IgE increased the PPV to 75% for any reaction. For this calculation, the number of patients with a positive challenge who had both food-specific IgE and a positive patch test were divided by patients with both a positive IgE and APT, irrespective whether they had reacted to the challenge or not. Calculation for single foods was not performed due to the low number of patients with a combined positive APT and specific IgE.

Discussion

The role of food as a provocation factor of AD has been discussed extensively during the last decades. Atherton et al. observed a significant improvement of dermatitis in children during a period of a placebo-controlled diet [16]. Several open studies also describe some benefit in a subpopulation of patients with AD, but a major problem of these studies is their open design, which does not exclude placebo effects [25].

We found that 46% of all oral challenge tests resulted in an immediate and/or late eczematous reaction and based on these results, food allergy was diagnosed in 64% of the investigated children. These high numbers may result from the pre-selection of the children investigated in our study, who were suspected of food allergy by their history or positive food-specific IgE/APT. Moreover, the foods used for the challenge procedures are known to induce most of the allergic reactions in children with AD [11, 13, 26]. Similarly, in a study by Niggemann et al. [14], 51% of all challenge tests resulted in an allergic reaction and 81% of all patients reacted to at least one allergen. Sampson and Alberg found a frequency of food allergy of more than 60% in children with AD [18, 27]. The frequency of food allergy in children with AD was estimated at 30% in a study by Burks et al. who investigated infants who were not specifically referred for the evaluation of food allergy [26]. Children included into this study were older than children investigated in our study. About one-third of children will outgrow their food allergy after 1–2 years under allergen avoidance, dependent on the kind of food [15]. Differences in the proportion of children

reacting to food challenge may not only be due to pre-selection, but also to the method used for DBPCFC. In the studies by Niggemann et al. [14], Burks et al. [26], Sampson [27] and Sampson and Albergo [18], the food was not given repetitively over 2 days. Each day two challenges (verum/placebo) were administered within 4 h in the trials by Sampson and Burks, and thus the patients were not observable for longer periods than 1 day. Moreover, different preparations of food were used. Similar as in our study, cow's milk, wheat powder and soy milk were administered by Niggemann et al. [14]. Instead of egg powder consisting of egg white and yolk as it was administered in our study they used raw egg. Dehydrated food mixed with juice was used in the studies by Burks and Sampson.

Whether eczematous lesions can be induced by the ingestion of food is still a matter of debate. There are few studies in the literature that differentiate food-induced eczema occurring after many hours clearly from immediate-type reactions, which may be due to the fact that most investigators did not observe the patients for longer periods than 1 day upon challenge. In order to distinguish eczematous responses clearly from early cutaneous reactions, the suspected food was given over a period of 2 days and the next food was introduced after a challenge-free day in our trial. The cutaneous inflammatory infiltrate in eczematous lesions of patients with AD consists mainly of CD4⁺T cells and food allergen-specific T cells have been shown to be involved in the late eczematous response to food [6, 8, 9].

Due to the pathophysiological mechanisms involved into food-induced eczema, eczematous lesions usually need at least 6 h to develop, and therefore, we defined late eczematous reactions as occurring later than 6 h after ingestion of food. More than 50% of all positive oral challenges were associated with an exacerbation of eczema in our study. Isolated eczematous reactions were seen in 12% of all positive challenges. Fifty percent of the isolated eczematous reactions occurred after challenge with wheat, but the limited number of patients reacting in this way may bias these results. We did not observe any late gastrointestinal or respiratory reaction, which may be explained by the selection of children referred for the evaluation of AD. Niggemann et al. observed late reactions in 25% of positive provocation tests [14]. However, late reactions were defined as symptoms occurring after more than 2 h in their study, thus including probably not only eczematous reactions, which generally need at least 6 h to develop. Other investigators did not observe true eczematous reactions upon DBPCFC [18, 26], which may be due to the challenge method described above. In these studies cutaneous symptoms as pruritus and rash occurred always within 2 h upon challenge. Such immediate-type symptoms may be induced by mast cell degranulation with subsequent release of pro-inflammatory mediators like histamine. Interestingly, 19% of all immediate reactions occurred on the second challenge day after the highest dose had been tolerated on the first day in our study. The pathophysiological mechanism of this phenomenon is not clear, but repetitive doses may booster the food-specific allergic response. Delayed immediate reactions occurring in 16% of our patients after 2–6 h are thought to be induced by mediators derived from mast cells like leucotriens and cytokines, leading to an influx of eosinophils, basophils and neutrophils [28, 29].

To date, there are no diagnostic tools that will reliably predict or exclude allergic reactions to food. Anamnestic data are usually reliable for the identification of clear immediate-type responses to food. We found a low predictive accuracy of the personal history particularly for eczematous reactions, which need several hours to develop.

Specific IgE levels associated with a positive challenge test were significantly higher than specific IgE levels associated with a negative challenge in our patients, an observation which is in keeping with the results of others [14]. The fact that sensitivity, specificity and PPV of food-specific IgE were higher for immediate than for eczematous reactions underlines the importance of food-specific IgE particularly for immediate reactions. From a physician's point of view the PPV are of greatest interest, because they indicate how likely the patient will develop a clinical reaction to a certain food. The PPV of food-specific IgE was only 33% for eczematous reactions, which means that only one-third of all challenges associated with food-specific IgE resulted in exacerbation of AD. The PPV of food-specific IgE was 57% for immediate reactions. This result is consistent with a previous study by Sampson and Albergo, who found the PPV ranging from 18% to 57% for different kinds of food [18]. The diagnostic accuracy of food-specific IgE was lower in children who were older than 2 years compared with younger children, which is most likely explained by the fact that many children outgrow their food allergy, while food-specific IgE remains detectable [15]. The probability of a positive immediate reaction to food has been shown to depend on the level of food-specific IgE and for foods such as cow's milk and hen's egg it is possible to determine IgE levels which predict clinical reactivity with 95% certainty in children with AD [30, 31]. The number of DBPCFC performed in our study did not allow to calculate reliable diagnostic decision points for food-specific IgE.

Twenty-five percent of all positive challenges were associated with negative food-specific IgE in our trial, and food-specific T cells may play a predominant role in the pathogenesis of these reactions. A relatively high number of patients without food-specific IgE, who had a history suggestive of food allergy or a positive APT were included into our analysis, which might have resulted in the relatively high number of positive challenges associated with negative food-specific IgE. Thus the suspicion of food allergy rather than the detection of food-specific IgE should be the indication for DBPCFC in children with moderate and severe AD. Similarly as Niggemann et al., who found that 10% of positive DBPCFC were not associated with food-specific IgE [32], there were no differences in terms of age and total IgE levels as compared with children with food-specific IgE. The proportion of isolated/combined eczematous reactions was slightly higher for the challenges associated with negative food-specific IgE in our study. Interestingly, some patients who had no food-specific IgE showed isolated immediate reactions.

Since APT lesions resemble spontaneous lesions both clinically and histologically, APT are likely to mimic the mechanisms involved into food/aeroallergen-responsive AD. In fact, 75% of our patients with an isolated eczematous reaction had a positive APT. In five patients with a positive challenge who had no food-specific IgE an APT was performed and resulted in a positive reaction suggesting a

major role of food-specific T cells. However, the pathophysiological mechanism leading to eczema is not clear in these patients. The low specificity and PPV may result from the many false positive APT results. These were seen particularly after application of wheat gluten and are possibly caused by irritation. We had observed even more irritative reactions before when whole-wheat powder had been used for APT in patients suffering from AD (data not shown). The APT with cow's milk allergy had a PPV of 95% in a study by Roehr et al. [20]. The combination with positive food-specific IgE of any level resulted in a PPV of 100% for early and late reactions. Other investigators found a markedly lower PPV of 40% for immediate reactions to cow's milk, but did not investigate late reactions [22]. Isolauri and Turjanmaa found a correlation between positive patch test results and late reactions to cow's milk [33]. In another study focusing on wheat allergy the PPV was 63% [21]. To date, the APT is not well standardized, and different methods in preparing the test solutions are likely to cause controversial results. Therefore, further studies are needed before the APT may be used as a routine tool for the diagnosis of food allergy.

The data presented come from a retrospective analysis of 106 DBPCFC performed in our department for the evaluation of potential trigger factors in children with AD. Thus, uniform inclusion criteria could not be defined, which renders the interpretation of the data difficult in some aspects. In most of the children food-specific IgE was detected, either alone or in combination with a positive APT reaction or a history suggestive of food allergy. On the other hand, in some children no food-specific IgE was detectable, since this was not an inclusion criterion for a DBPCFC. This may have resulted in less positive challenge reactions than expected in a homogenous cohort of children sensitized to the challenged food.

Despite these difficulties some conclusions can be drawn from our study: allergic reactions to food are often observed in patients with AD. The relatively high number of patients showing an eczematous response suggests that food allergy should be excluded in any child with AD who does not respond appropriately to therapy. However, one should always bear in mind, that several other factors than food have an influence on the course of eczema in patients with AD. The personal history, food-specific IgE and the APT are not reliable enough for the identification of clinically relevant foods, particularly when eczematous reactions are concerned. Therefore, food challenges are still necessary for the appropriate diagnosis of food allergy in patients with AD. Elimination diets based solely on *in vitro* or skin tests are inadequate, if the history is not convincing. A negative open challenge may confirm the absence of food allergy, in positive cases, a DBPCFC is recommended.

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