

Predictors of positive food challenge outcome in non-IgE-mediated reactions to food in children with atopic dermatitis

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Background: Atopic dermatitis is frequently associated with food allergy. In general, clinically manifested food allergy is regarded as IgE mediated. However, there are some children with food allergy for whom IgE hypersensitivity cannot be proven.

Objective: The aim was to evaluate the percentage of children with positive double-blind, placebo-controlled food challenge (DBPCFC) results but without any proof of IgE sensitization and to characterize this subgroup of children.

Methods: Two hundred eight DBPCFCs were performed in 139 children (median age, 13 months) with atopic dermatitis and suspected food-related clinical symptoms. All children were subjected to skin prick tests (SPTs), determination of specific IgE, and atopy patch tests.

Results: One hundred eleven (53%) of 208 oral food challenge results were assessed as positive. Positive challenge results were separated into 2 groups according to IgE positivity: negative SPT and negative specific IgE results in serum (group A, $n = 12$) and positive SPT, specific IgE, or both results in serum (group B, $n = 99$). The atopy patch test results; the distribution of early, late, or both clinical reactions; the age of the children; and the total IgE levels all showed no significant differences between the 2 groups. However, wheat challenge results were more often positive among the apparently non-IgE-sensitized children, and hen's egg challenge results were more often positive in the sensitized group ($P < .05$).

Conclusion: Around 10% of positive DBPCFC results are not IgE mediated. Therefore not the proof of specific IgE but the suspicion of food-related symptoms should be the indication to perform oral food challenges, especially in the case of wheat. Otherwise, some children will not receive diagnoses for food allergy and be denied the benefits of a specific diet. (*J Allergy Clin Immunol* 2001;108:1053-8.)

Key words: Allergy; atopy patch test; children; cow's milk; double-blind, placebo-controlled food challenge; food challenge; hen's egg; sensitization; skin prick test; specific IgE

Abbreviations used

AD:	Atopic dermatitis
APT:	Atopy patch test
CM:	Cow's milk
DBPCFC:	Double-blind, placebo-controlled food challenge
HE:	Hen's egg
SPT:	Skin prick test

Atopic dermatitis (AD) is frequently associated with food allergy.¹ The number of children with clinically relevant food allergy is reported to be around 40%.²⁻⁴ Among the most commonly offending foods are cow's milk (CM), hen's egg (HE), and wheat.^{3,4} AD and food allergy are diseases with a predominance in early childhood.^{5,6} Clinical reactions to food range from mild skin symptoms to life-threatening anaphylactic reactions.⁷⁻⁹

The diagnostic work-up of suspected food allergy includes skin prick tests (SPTs),¹⁰ the measurement of food-specific IgE antibodies with serologic assays,^{11,12} and, more recently, the atopy patch test (APT).¹³⁻¹⁵ Although a positive SPT response seems to reflect early reactions (eg, urticaria) to food challenges,¹³ the APTs have shown efficacy for late-phase clinical reactions (eg, exacerbation of eczema).¹³⁻¹⁵

In general, clinically manifested food allergy is regarded as IgE mediated. However, there are some cases in which IgE can not be proved, either by means of SPT or measurement of specific IgE in serum. The aim of this study was first to evaluate the percentage of children with positive double-blind, placebo-controlled food challenge (DBPCFC) results to CM, HE, or wheat but with no proof of IgE sensitization and second to characterize this subgroup of children by looking for predictors.

METHODS

Patients

We retrospectively reviewed 208 oral provocations in 139 children (74 boys and 65 girls) consecutively admitted to our ward for diagnosis of suspected food allergy. Ages ranged from 2 months to 11.2 years (median, 13 months). All children had AD, as defined by the criteria of Sampson¹⁶ and Seymour et al¹⁷ and modified from the method of Hanifin and Rajka.¹⁸

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Received for publication July 2, 2001; revised September 5, 2001; accepted for publication September 14, 2001.

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0091-6749/2001 \$35.00 + 0 1/87/120192

doi:10.1067/mai.2001.120192

Scoring of AD

Severity of eczema was scored according to the SCORAD score,¹⁹ with assessment of topography items (affected skin area), intensity criteria (extent of erythema, edema, crusts, excoriations, lichenification, and xerosis), and subjective parameters (itchiness and loss of sleep). The maximum possible score was 103 points. Eighty-two (59%) children had mild AD (SCORAD score, 25 points), 45 (32%) had moderate AD (SCORAD score, 26-49 points), and 12 (9%) had severe AD (SCORAD score, 50 points).

Skin prick test

Fresh foods were applied to the patient's volar forearm (ie, fresh CM containing 3.5% fat, whisked native HE, and wheat powder [Kröner, Ibbenbüren, Germany] was dissolved in 1 g/10 mL water). SPTs were performed with a 1-mm single-peak lancet (ALK, Copenhagen, Denmark). Reactions were read at 15 minutes, and the SPT response was assessed as positive if the wheal was 3 mm or larger without reaction of the negative control (NaCl 0.9%). All responded to 10 mg/mL histamine dihydrochloride (ALK) used as a positive control.^{8,9}

Atopy patch test

One drop (50 mL) of fresh CM containing 3.5% fat, of whisked HE (white of egg and yolk), and of wheat powder (Kröner) dissolved in water (1 g/10 mL) was put on filter paper and applied to the unaffected skin of the child's back with 12-mm aluminum cups on adhesive tape (Finn Chambers on Scanpor; Hermal, Reinbek, Germany). Application sites were checked after 20 minutes for immediate reactions. The occlusion time was 48 hours, and results were read 20 minutes after removal of the cups and again 24 hours later for the final evaluation of the test. After 72 hours, reactions were classified as positive if there was erythema together with infiltration.^{14,15} Irritant reactions (sharply defined brownish erythema, decrescendo phenomenon, blistering, and lack of clear infiltration) were not regarded as positive.

Determination of specific IgE antibodies

Blood was drawn before food challenge. Patient sera were analyzed for concentrations of total IgE and specific IgE antibody titers to CM, HE, wheat, and soy, as determined by means of FEIA with the Pharmacia CAP system (Kabi-Pharmacia, Uppsala, Sweden).²⁰ The detection limit of the CAP system is 0.35 kU/L IgE; children were regarded as sensitized if specific IgE levels were above the detection limit. Lesser levels of food-specific IgE may be present in the patients labeled as non-IgE sensitized.

Food challenges

Inclusion criteria for performing oral food challenges were suspicion of food-related symptoms by parents, physicians, or both. Children taking an antihistamine (solely cetirizine) were advised to avoid it 72 hours before provocation. Topical glucocorticosteroids were allowed twice daily at a concentration of 1% hydrocortisone or 0.1% betamethasone. All food challenges were performed in a double-blind, placebo-controlled manner.²¹ Randomization and preparation of the challenges were performed by the clinical dietician. Briefly, every 20 minutes, successive doses (0.1, 0.3, 1.0, 3.0, 10.0, 30.0, and 100.0 mL) of fresh pasteurized CM containing 3.5% fat, soy milk, and wheat powder (Kröner; total of 10 g of wheat protein) or placebo (Neocate SHS, Liverpool, United Kingdom) were administered. Raw HE was given in a similar way, except that the highest dose was omitted. Full emergency equipment, including antihistamines, glucocorticosteroids, and β -agonists, was at hand. The provocation was stopped if clinical symptoms were observed or the highest dose was reached. The children were observed as inpatients for 48 hours after each challenge (allergen and placebo).

The food challenge results were scored as positive by a pediatric allergy specialist (SR or CCR) if one or more of the following objective clinical reactions were noted: urticaria, angioedema, wheezing, vomiting, diarrhea, abdominal pain, shock, or exacerbation of eczema. Early reactions were defined as clinical symptoms within 120 minutes after administering the highest dose and late reactions if symptoms occurred after more than 2 hours. For presentation and calculation of data, combined reactions were added to late-phase reactions.

Statistical analyses

We used SPSS for Windows (version 10.0; SPSS, Chicago, Ill). The χ^2 test (Pearson) was used for categoric data (early and late reactions, APT, and allergens) to calculate differences between groups. For continuous nonparametric data (age and total IgE level), the Mann-Whitney *U* test was used. Statistical significance was defined by a 2-sided *P* level of .05.

RESULTS

Outcome of oral food challenges and allergologic tests

We analyzed a total of 208 DBPCFCs performed in 139 children: 101 (73%) children were challenged with CM, 58 (42%) with HE, and 49 (35%) with wheat. All 139 patients were subjected to DBPCFCs, SPTs, APTs, and determinations of allergen-specific IgE antibodies. Total IgE levels ranged from 1.2 kU/L to 11,325 kU/L (mean, 442 kU/L).

Of 208 challenges, 111 (53%) results were assessed as positive: 52 (47%) CM, 38 (34%) HE, and 21 (19%) wheat challenges. The distribution of early-phase (0-120 minutes after provocation) and late-phase reactions (3-48 hours after provocation) and the pattern of clinical reactions are shown in Fig 1.

For further calculations, children with positive oral food challenge results (*n* = 111) were divided into 2 groups (Fig 2). Group A comprised all children with negative SPT and specific IgE results in serum (*n* = 12). Group B comprised children with a positive SPT result, proof of specific IgE in serum, or both (*n* = 99). According to this, 10.8% of children with positive oral food challenge results had no proof of IgE positivity.

Atopy patch test

The APT was positive in 7 (58%) of 12 challenge results in apparently non-IgE-sensitized children and in 39 (39%) of 99 challenge results in the sensitized group. However, this difference was not statistically significant (*P* = .208).

Early- and late-phase reactions

In group A, 5 (42%) of 12 children showed only an early clinical reaction, and 7 (58%) children showed a late or combined clinical reaction during oral food challenge. In group B, 54 (55%) of 99 children showed an early reaction, and 45 (45%) children showed a late or combined reaction. Again, this difference was not statistically significant (*P* = .398).

Allergens

Taking all 3 allergens together, 12 (10.8%) children with positive oral food challenge results had no proof of

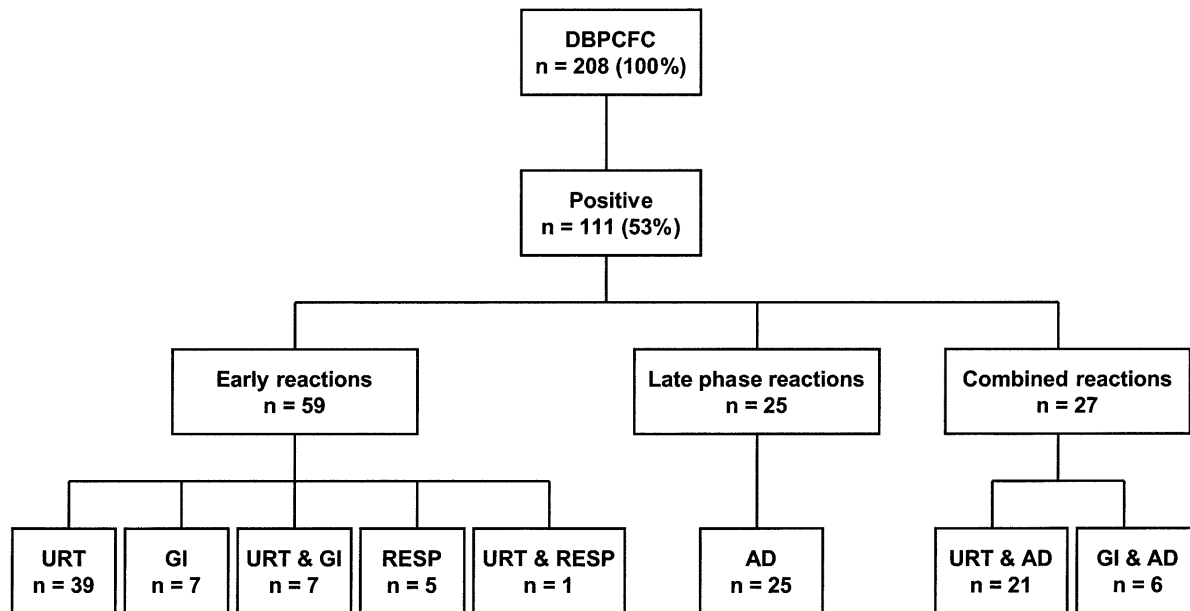


FIG 1. Clinical pattern of food-induced reactions after DBPCFCs in children with AD and suspected food allergy. *URT*, Urticaria; *GI*, gastrointestinal; *RESP*, respiratory.

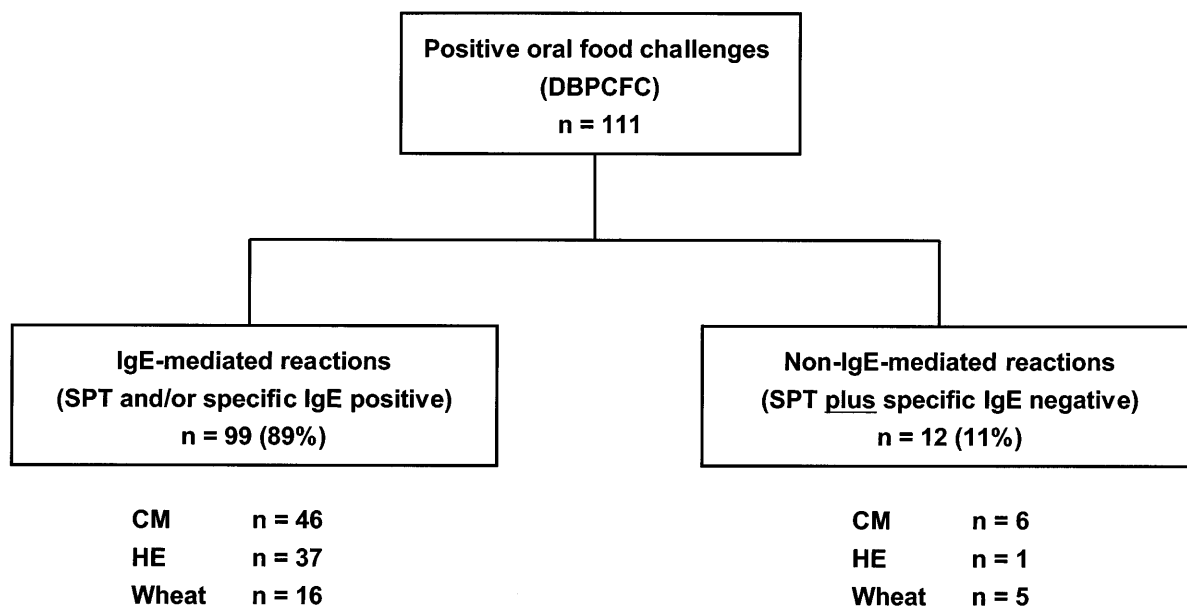


FIG 2. Pattern of positive food challenge results according to IgE sensitization.

IgE positivity. Calculating differences for the percentages of positive oral food challenge results for the 3 allergens, there was a significant difference ($P = .042$, Fig 3). Wheat provocation results ($5/21 = 23.8\%$) were more

likely positive among the apparently non-IgE-sensitized children (group A), whereas HE results ($37 [97.4\%]$ of 38) were more often positive in the sensitized children (group B).

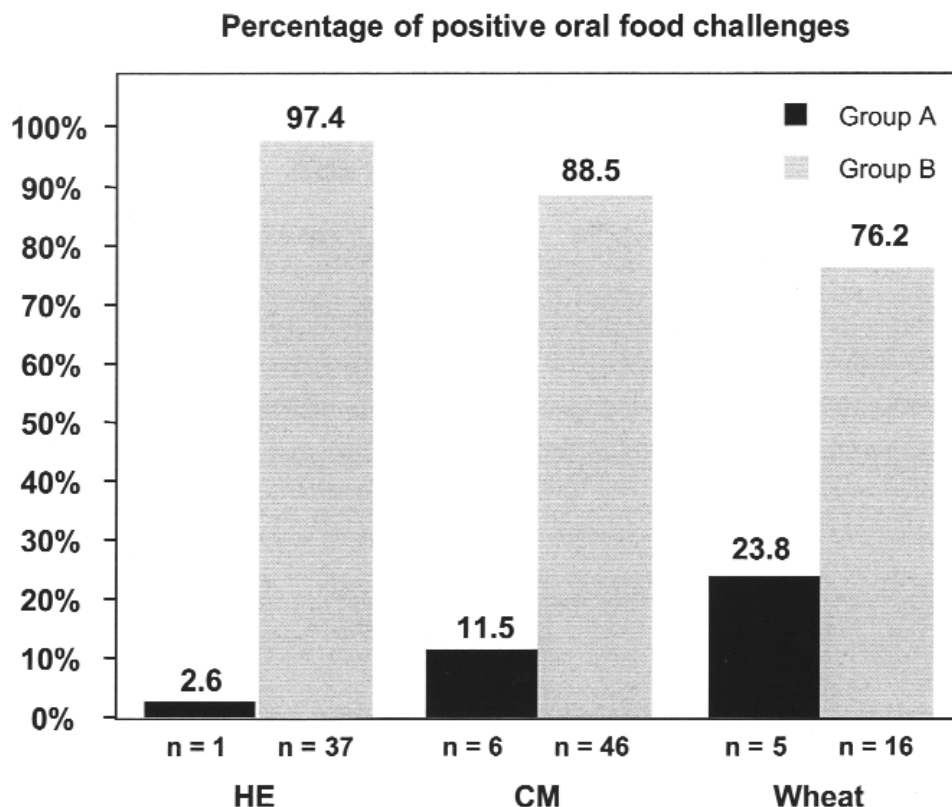


FIG 3. Percentage of positive oral food challenge results in apparently non-IgE-sensitized children (group A) and sensitized children (group B, $P = .042$).

Age of children

The ages in group A ranged from 7 to 77 months (median, 14 months), and those in group B ranged from 2 to 119 months (median, 14 months; $P = .576$, not significant).

Total IgE

The total IgE in the apparently non-IgE-sensitized children (group A) ranged from 15.0 to 796 kU/L (median, 51 kU/L), and that in sensitized children (group B) ranged from 2.0 to 11,325 kU/L (median, 100.0 kU/L; $P = .078$, showing a trend). Seven of 11 positive oral challenge results were negative for SPTs, IgE determinations, and APTs. When comparing these 7 challenges with results in group B (sensitized children), the difference became statistically significant ($P = .02$).

DISCUSSION

Two hundred eight oral food challenges were performed in 139 children, of which 111 provocation results were assessed as positive. In 12 (10.8%) cases no specific IgE could be found for the corresponding allergen. This

result seems astonishing because in general, positive oral food challenge results are regarded as IgE mediated. Several questions may be raised in view of our results.

Clinically relevant food allergy was shown by means of oral food challenges. Provocations were performed as DBPCFCs, which still represent the gold standard for diagnosis of food allergy.^{4,12,21,22} Furthermore, no placebo reaction was positive in this series, which may support the validity of the observed outcomes of the challenges.

The grouping into sensitized and apparently non-IgE-sensitized children with positive DBPCFC results was ensured by the corresponding definition criteria. Group A (apparently non-IgE-sensitized children) comprised children with a negative SPT response plus a negative specific IgE result in serum, and group B (sensitized children) consisted of children with a positive SPT response, positive proof of specific IgE in serum, or both. This confirmative procedure was chosen because it is believed that there is about 10% of discrepancy in the literature between in vivo and in vitro determinations of specific IgE.

We expected that apparently non-IgE-sensitized children (group A) would show a positive APT response sig-

nificantly more often and would be more likely to have late-phase clinical reactions because it has recently been shown that the APT has a good positive predictive value for late-phase reactions.^{13-15,23} However, although there was a tendency toward these results, it did not reach statistical significance. One reason may be the relatively small number of children (n = 12) in the apparently non-IgE-sensitized group.

Our results indicate that positive challenge results seem to be significantly more likely to occur in the apparently non-IgE-sensitized group to wheat compared with to HE and CM. Other studies have also found that there is no specific IgE to wheat in many cases of challenge-proven wheat allergy (in which the APT result is positive).²⁴ Children with suspected allergy to wheat should therefore be considered for DBPCFC, even in the absence of specific IgE. On the other hand, HE was more often represented in IgE-mediated clinical reactions, which is in keeping with previous observations showing that HE allergy presents primarily with immediate-type reactions.⁴ There is a higher prevalence of life-threatening anaphylactic reactions to HE than to other allergens.⁴ No statement can be made from our data for other allergens (eg, fish, peanut, and tree nut), which may also account for a significant number of food allergies in children with AD.

It remains unclear which mechanisms lead to clear-cut early- or late-phase allergic reactions during DBPCFCs. In addition to IgE-mediated reactions, which still play an important role,^{15,25} lymphocytes seem to be involved in food allergy in children²⁶⁻²⁸ and adults.²⁹ Supporting our clinical findings, it has been reported that lymphocyte proliferative responses to food allergens in patients with AD may be positive in children without IgE sensitization.³⁰ However, lymphocyte proliferation assays are neither diagnostic nor predictive of clinical reactivity in individual patients.³¹

Furthermore, AD as the underlying disease may itself give a clue because most studies investigating the role of lymphocyte-mediated food reactions (including this one) were performed with children with AD, and lymphocytes are known to contribute to the pathogenesis of AD. However, it could be shown that both infants with AD with or without CM allergy had a CM-specific T-helper-cell response, although with a different cytokine profile.³² Further studies of children without AD and challenge-proven food allergy without evidence of IgE sensitization are warranted to unravel this mystery.

In the literature other authors have emphasized the need to challenge any patient suspected of an allergic reaction to food, regardless of laboratory findings^{1,22}; however, no data are thus far available concerning the frequency of negative laboratory test results in patients with DBPCFC-proven reactions to food. Our results indicate that around 10% of positive oral food challenge results in children with AD are not IgE mediated. Therefore not the proof of specific IgE but the suspicion of food-related symptoms should be the indication to perform oral food challenges, especially in the case of

wheat. Otherwise, some children will not receive a diagnosis of food allergy and be denied the benefits of a specific diet.

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