

Original article

The atopy patch test (APT) – a useful tool for the diagnosis of food allergy in children with atopic dermatitis

Background: While immediate-type clinical reactions to food can quite easily be identified by history or measurement of specific IgE in combination with positive oral food challenges, the evaluation of food allergy in the absence of immediate clinical reactions still presents diagnostic difficulties – particularly in children with atopic dermatitis. The objective of this study was to evaluate the diagnostic value of the atopy patch test (APT) with regard to late-phase reactions observed in double-blind, placebo-controlled food challenges with cow's milk, hen's egg, wheat, and soybean.

Methods: We investigated 75 children (median age 2.1 years) with suspected food allergy by double-blind, placebo-controlled food challenges, specific IgE in serum, skin prick test, and APT. Of the subjects, 69/75 suffered from atopic dermatitis.

Results: Of 209 oral challenges, 133 were performed with allergen and 76 with placebo. We assessed 77/133 allergen and 2/76 placebo challenges as positive. In 66 of 77 (86%) positive oral challenges, specific IgE in serum to the corresponding allergen was positive; in 64/77 (83%) the skin prick test, and in 42/77 (55%) the APT was positive. While immediate-type reactions were associated with positive skin prick test and proof of specific IgE in serum, late-phase clinical reactions were associated with a positive APT (sensitivity 76%, specificity 95%).

Conclusions: The APT seems to be a valuable additional tool in the diagnostic work-up of food allergy in children with atopic dermatitis – especially with regard to late-phase clinical reactions. The APT may help to prevent unnecessary restrictive diets which may be the consequence of misjudging late reactions by clinical assessment alone.

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Atopic dermatitis (AD) is one of the most common and troublesome chronic diseases in children. Food allergy has been demonstrated to play an important role in the pathogenesis of AD, affecting around one-third of the children with AD (1). While immediate-type clinical reactions to food can quite easily be identified by history or measurement of specific IgE in combination with positive double-blind, placebo-controlled oral food challenge (DBPCFC), the evaluation of food allergy in the absence of immediate clinical reactions still presents diagnostic difficulties – particularly in polysensitized children with AD (2).

The atopy patch test (APT) as an epicutaneous test using type 1 allergens has been proposed and studied for

aeroallergens (3–7). The patch test reaction to aeroallergens is specific for sensitized AD patients, and does not occur in healthy volunteers or in patients suffering from asthma or rhinitis (3). T-cell responses seem to play a role in both lesional skin of AD patients and skin from APT reactions with aeroallergens (7). Furthermore, the close macroscopic and microscopic similarities between the specimens from APT sites and lesional skin of patients with AD indicate that the APT is a valid model to study allergic inflammation in AD (6).

Little is known about the value of the APT with respect to food allergens. The hypothesis of this study was that the skin prick test (SPT) and specific IgE in serum may reflect early clinical reactions (within 2 h) to the offending food, while the APT may have a high predictive capacity for late-phase clinical reactions during the DBPCFC (8).

Therefore, this study aimed to evaluate the predictive value of the APT in terms of late-phase clinical reactions observed during DBPCFC with cow's milk

Abbreviations. AD: atopic dermatitis; APT: atopy patch test; CAP: specific IgE by Pharmacia CAP FEIA System; CM: cow's milk; DBPCFC: double-blind, placebo-controlled food challenge; HE: hen's egg; IgE: immunoglobulin E; NPV: negative predictive value; PPV: positive predictive value; SPT: skin prick test.

(CM), hen's egg (HE), wheat, and soybean in children with AD.

Material and methods

Patients

Seventy-five children (34 girls, 41 boys) were included in the study. Ages ranged from 4 months to 12.5 years (median age 2.1 years). Sixty-nine children suffered from AD as defined by the criteria of Sampson (9) and Seymour et al. (10) modified from Hanifin & Rajka (11).

Inclusion criteria for the 75 children were suspicion of food-related symptoms by parents or physicians. Six additional children could not be included due to clinically relevant reactions with acute local urticaria and itching 5–15 min after administration of the APT with egg.

Study design

On an inpatient basis, children were challenged in a DBPCFC manner. When necessary, skin was cleared before starting the DBPCFC. Blood was sampled before the study for determining specific IgE to common foods, including CM, HE, wheat, and soybean. SPT and APT were performed during the DBPCFC with the identical native allergens. The physician responsible for the DBPCFC was blinded to the results of the APT and specific IgE in serum, and vice versa. The study protocol was approved by the local ethics committee.

DBPCFC

Oral food challenge was performed in a double-blind, placebo-controlled clinical fashion as previously described (12). Briefly, every 48 h, 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 and soybean milk or placebo (Neocate®, SHS, Liverpool, UK) were administered. Raw HE (egg white and yolk) and wheat powder (Körner, Ibbenbüren, Germany) dissolved in water (total amount 10 g of wheat protein) were given in a similar regimen (ml) as for CM, except that the highest dose (100 ml) was not administered. The time interval between each dose was 30 min. During the whole stay at our hospital, the children were on an exclusion diet using an extensively hydrolyzed casein formula or an amino-acid-based formula.

Provocation was stopped if clinical symptoms were observed or the highest dose was reached. The children were observed for up to 48 h after each allergen or placebo challenge on an inpatient basis. The food challenges were scored as positive if objective clinical reactions were observed such as urticaria, angioedema, wheezing, vomiting, diarrhea, abdominal pain, or exacerbation of eczema. An increase of the SCORAD

score of at least 10 points was used for defining exacerbation of AD. Antihistamines were withdrawn at least 3 days prior to challenge. Topical corticosteroids were allowed twice a day at a concentration of 1% hydrocortisone or 0.3% betamethasone valerate, but not 48 h before APT on the back. Early reactions were defined as clinical symptoms if they appeared within 2 h after administration of the highest dose; late ones if symptoms occurred after >2 h.

Severity scoring of AD

Severity of eczema was scored according to the SCORAD index (13), with assessment of “topography” items (magnitude of skin area), “intensity” criteria (extent of erythema, edema, crusts, excoriations, lichenification, and dryness), and, subjective parameters (extent of itch and loss of sleep). The maximum possible score was 103 points.

Determination of serum IgE (CAP)

Concentrations of total IgE and specific IgE to CM, HE, wheat, and soybean in serum were determined by FEIA with the Pharmacia CAP System (PCS) (Pharmacia & Upjohn, Uppsala, Sweden) (14). The detection limit was 0.35 kU/l IgE; children were regarded as sensitized if specific IgE was above detection limit.

SPT

The SPT was performed on the volar forearm with fresh CM containing 3.5% fat, native HE (egg white and yolk), and wheat powder (Körner, Ibbenbüren, Germany) dissolved in water (1 g/10 ml), and soybean milk. Reactions were read at 15 min, and the SPT was assessed as positive if the wheal was ≥ 3 mm without reaction of negative control. As the positive control, 10 mg/ml histamine dihydrochloride (ALK, Copenhagen) was used.

APT

The APT with CM, HE, wheat, and soybean was performed in all children during hospitalization on uninvolved skin of the children's backs with 12 mm aluminum cups (Finn Chambers on Scanpor, Hermal, Reinbek, Germany). One drop of fresh CM containing 3.5% fat, native HE (egg white and yolk), and wheat powder (Körner, Ibbenbüren, Germany) dissolved in water (1 g/10 ml), and soybean milk were put on the filter paper. The occlusion time was 48 h, and results were read 20 min and 24 h after removal of the cups. After 72 h, reactions were classified as positive if erythema plus clear infiltration occurred. The APT was read with a classification of + for erythema and slight infiltration, ++ for erythema and papules, and +++ for erythema and vesicles. To exclude false

Table 1. Evaluation of predictive capacity of specific IgE in serum, SPT, and APT for early- and/or late-phase clinical reactions to allergen challenges ($n=133$)

	Sensitivity	Specificity	PPV	NPV
Specific IgE in serum	86%	29%	62%	59%
Skin prick test	83%	70%	79%	75%
Atopy patch test	55%	95%	93%	60%

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

positive reactions, all allergens were tested in a 1:10 solution at the same time.

Predictive capacity

Sensitivity was defined as the proportion of true positives detected, specificity as the proportion of true negatives detected, positive predictive value as the proportion of symptomatic individuals among test positives, and negative predictive value as the proportion of nonsymptomatic individuals among test negatives.

Results

Clinical outcome of DBPCFC

Complete data of DBPCFC and SPT, APT, and specific IgE in serum could be obtained from 75 children. A total of 209 oral challenges were performed on these children. The ratio of allergen ($n=133$) to placebo challenges ($n=76$) was 1.75:1. Of the 133 oral challenges with allergen, 54 were performed with CM, 41 with HE, 23 with wheat, and 15 with soybean. Total IgE ranged from 2 to 11 325 kU/l (median 491 kU/l). SCORAD scores ranged from 0 to 79 points (median 26 points).

Exactly 77/133 (58%) oral allergen challenges and 2/76 (2.6%) placebo challenges were assessed as positive (Fig. 1). Of the 77 positive reactions, 27/41 (66%) were observed with HE, 35/54 (65%) with CM, 11/23 (48%) with wheat, and 4/15 (27%) with soybean. Exactly 39/77 (51%) children with positive allergen provocations showed early clinical reactions, 21 (27%) showed late

reactions, and 17 (22%) combined early and late clinical reactions (Fig. 2). Of the early reactions, 19 (49%) children showed skin symptoms (urticaria, worsening of eczema with erythema, and itch), four (10%) skin and gastrointestinal symptoms, 13 (33%) gastrointestinal symptoms (recurrent vomiting and diarrhea), and three (8%) respiratory symptoms (inspiratory stridor and wheezing). All late reactions were exacerbation of eczema, and in all combined reactions eczematous reactions were included.

APT, SPT, and specific IgE in serum

In 66/77 (86%) oral challenges, specific IgE in serum to the corresponding allergen was positive; in 64/77 (83%), the SPT was positive; and in 42/77 (55%), the APT was positive. Table 1 summarizes the data of sensitivity, specificity, positive predictive value, and negative predictive value for specific IgE in serum (CAP), SPT, and APT, if positive, negative, early, late, and combined clinical reactions to oral challenges are considered. Focusing on early clinical reactions (Table 2) and on late clinical reactions (Table 3) revealed different results for the predictive capacity of the IgE in serum, SPT, and APT. In comparison of the four allergens, sensitivity and specificity did not show significant differences. The APT results were not dependent on the level of specific IgE to the corresponding allergen.

No adverse reactions could be observed to the adhesive used to fix the aluminum cups on the backs of the children. For determination of whether late reactions could occur after SPT, the SPT site was assessed on the next day. No skin reactions were found 24 h after the allergen had been applied.

Discussion

In our study, sensitivity of the APT for late-phase clinical reactions was 76% and specificity was 95%, while corresponding figures for the SPT were 58% and 70%, and for the specific IgE in serum 71% and 29%, respectively.

Allergens for DBPCFC were chosen individually according to diagnostic needs. However, SPT and APT were performed with all four allergens in all children in

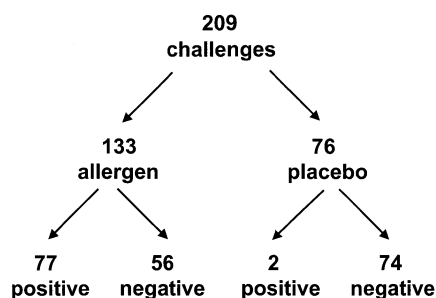


Figure 1. Outcome of oral challenges.

Table 2. Evaluation of predictive capacity of specific IgE in serum, SPT, and APT for early clinical reactions ($n=39$)

	Sensitivity	Specificity	PPV	NPV
Specific IgE in serum	95%	29%	62%	59%
Skin prick test	95%	70%	69%	95%
Atopy patch test	33%	95%	81%	67%

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

Table 3. Evaluation of predictive capacity of specific IgE in serum, SPT, and APT for late-phase clinical reactions ($n=21$)

	Sensitivity	Specificity	PPV	NPV
Specific IgE in serum	71%	29%	37%	72%
Skin prick test	58%	70%	41%	81%
Atopy patch test	76%	95%	81%	93%

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

order to calculate sensitivity and specificity of the tests for all allergens. In order to allow uninfluenced reading of the skin tests, SPT and APT were performed during the first days of the DBPCFC. Therefore, the physician responsible for the reading did not know the result of the DBPCFC. In addition, data about specific IgE in serum were not available before the DBPCFC were unblinded.

Because there is little information about the optimum concentration of the food used for the APT and to exclude false positive results by irritative reactions, all allergens were tested in a 1:10 solution in parallel. We observed 18/77 (23%) positive results in the 10% diluted APT, and these were seen in the patients with the strongest reactions to the undiluted ones. Furthermore, all these patients showed late eczematous reactions in the DBPCFC, mostly ($n=10$) to wheat. This indicates that APT results are not biased by unspecific, irritative reactions. The good percentages of sensitivity and specificity for the APT may be explained by the fact that we used the same allergen source and concentration as for DBPCFC and SPT. Native food seems to be suitable for performing APT.

Six out of 75 study patients had no history of skin symptoms and, especially, did not suffer from AD: none of these children showed a positive APT. This indicates that the APT – as shown for inhalant allergens – only works in patients with AD, as stated before (3). Two out of 76 placebo reactions were assessed as positive; both children showed worsening of eczema 16 and 23 h after receiving the highest dose. These false positive challenge results reflect day-to-day variation of eczema and underline the need for performing oral challenges in a double-blind, placebo-controlled manner. Six additional children could not be included in the study because they showed clinically relevant reactions with acute local urticarial wheals and itching (contact urticaria) 5–15 min after administration of the APT. In these six cases, HE was the allergen.

While there are several studies on the APT with aeroallergens (3–7, 15, 16), only one group from

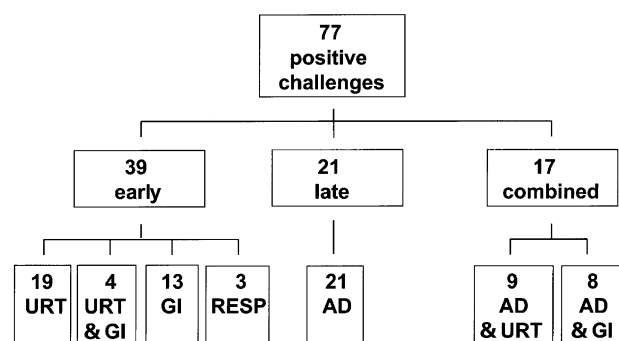


Figure 2. Clinical pattern of positive challenges. URT: urticaria; GI: gastrointestinal reactions; RESP: respiratory symptoms; AD: worsening of atopic dermatitis.

Finland has so far published data on the value of an APT with food (8, 17, 18). They studied infants 2–36 months of age (mean age 14 months) with CM allergy and found that parallel skin testing with combined prick and patch tests can enhance the accuracy in diagnosis of specific dietary allergies in children with AD. Our study indicates that age has no influence on the outcome, and the APT may as well be performed on older children. Furthermore, the predictive capacity of the APT is not restricted to CM but can also be demonstrated for HE, wheat, and soybean.

Specific IgE in serum showed a low specificity (29%) compared to the SPT (70%), a finding which may have two causes: firstly, as the sensitivity of the Pharmacia-CAP System is very high, the specificity correspondingly decreases; secondly, the SPT (and APT) were performed with native allergens (the same as those used in the oral food challenges), and this may explain the high specificity of the skin tests.

In AD – especially food-sensitive AD – T cells obviously play an important role, as shown in recent studies (19, 20). This investigation, showing that positive APT (with T-cell infiltration of the skin) correlate with clinical late-phase responses, supports the previous findings. Additional evidence from a recent study shows that APT reactions are associated with T-cell-mediated allergen-specific immune responses (7).

We conclude that the APT seems to be a valuable additional tool in the diagnostic work-up of food allergy in children with AD, especially with regard to late-phase clinical reactions. At this time, a positive APT does not make an oral challenge superfluous, but it helps to prevent unnecessary restrictive diets which may be the consequence of misjudging late reactions by clinical assessment alone.

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