

Evolving role of the atopy patch test in the diagnosis of food allergy

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The atopy patch test has developed into a valuable additional tool in the diagnostic work-up of food allergy in infants and children with atopic dermatitis. A positive atopy patch test may help to prevent imposing restrictive and unnecessary diets after misjudging late reactions by clinical assessment alone. Furthermore, the combination of positive atopy patch tests together with defined levels of specific IgE makes double-blind, placebo-controlled food challenges superfluous in some cases. However, several open questions indicate the need for further studies. *Curr Opin Allergy Clin Immunol* 2:253–256. © 2002 Lippincott Williams & Wilkins.

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Abbreviations

AD	atopic dermatitis
APT	atopy patch test
DBPCFC	double-blind, placebo-controlled food challenge
SPT	skin-prick test

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Introduction

IgE-mediated reactions to food have been shown to play an important role in the pathogenesis of atopic dermatitis (AD). The most relevant foods contributing to food allergy in infants and children are cows' milk, hen's egg, wheat, soy and peanut. In approximately one third of the children, foods seem to contribute to eczematous symptoms [1].

Whereas immediate-type clinical reactions to food (e.g. urticaria or bronchial obstruction 5–20 min after eating the food) can be identified quite easily, late-phase reactions (e.g. worsening of eczema after 24 h) still present diagnostic difficulties. Oral double-blind, placebo-controlled food challenges (DBPCFCs) are the gold standard in the diagnosis of food allergy [2]. However, even these challenges are not always easy to interpret, particularly in polysensitized children [3]. This indicates the need for new tools to improve the diagnosis of food allergy, especially in infants and children with AD.

History

The atopy patch test (APT) is performed epicutaneously. However, instead of using type IV allergens (such as metals or perfumes) typical immediate-type allergens are used (aeroallergens or foods).

Whereas the APT with aeroallergens (e.g. housedust mites) has been studied quite extensively, the first report on a possible role of the APT in food allergy came from a Finnish group [4,5]. The initial hypothesis was that the skin-prick test (SPT) and the measurement of specific IgE in serum may reflect early clinical reactions to the offending food (clinical symptoms within 2 h), whereas the APT may have a high predictive capacity for late-phase clinical reactions during DBPCFC [4,5].

Pathomechanism

The pathomechanism of the APT has not yet been studied in detail. The close macroscopic and microscopic similarities between the specimens from APT sites and the lesional skin of patients with AD indicate that the APT may be a valid model to study allergic inflammation in AD [6]. In food-sensitive AD in particular, T cells obviously play an important role, as shown in recent studies [7,8]. Our earlier clinical investigations [9•], indicating that positive APTs (with T cell infiltration of the skin) correlate with clinical late-phase responses, are in line with previous findings.

Additional evidence was provided by a study showing that APT reactions are associated with T lymphocyte-mediated allergen-specific immune responses [10]. A recent investigation has demonstrated that the chemokine pattern (CXCR3 activating chemokines) in skin biopsies can be used to distinguish between allergic and irritant patch test reactions [11]. Other authors have shown that a biphasic cytokine expression is typical for housedust mite allergen patch test reactions but not for irritant reactions [12].

Performance

APTs should be performed on uninvolved skin, usually on the child's back [9•]. Twelve millimetre aluminium cups (e.g. Finn chambers on Scanpor adhesive tape) should be used. One drop (50 µl) of fresh cows' milk (containing 3.5% fat), native whisked hen's egg (white of egg and yolk), wheat-powder dissolved in water (1 g/10 ml) or soy milk is put on the filter paper. Application sites should be checked after 15 min for immediate reactions.

The occlusion time is 48 h, and results are read 20 min after removal of the cups and again 24 h later for the final evaluation of the test. Final reactions (72 h) are classified as positive if there is erythema together with infiltration (Table 1). The APT should result in a clear yes or no answer. Positive reactions may be classified using + for erythema and infiltration, ++ for erythema and few papules, and +++ for erythema and four or more papules, ++++ erythema, many or spreading papules, +++++ erythema, papules and vesicles [13]. Irritant reactions (sharply defined brownish erythema, decrescendo phenomenon, blistering, lack of clear infiltration) are not positive.

Clinical studies

The first report on an APT with foods was published by Isolauri and Turkjanmaa [4], who showed that a positive APT reflects the late-phase reaction during oral food challenge in 183 cows' milk allergic children aged 2–36 months with AD. The authors stated that combined SPT and patch tests significantly enhanced the accuracy in the diagnosis of specific dietary allergies in children with AD.

Our group investigated 75 children (median age 2.1 years) with suspected food allergy using DBPCFCs,

specific IgE in serum, SPT and APT [9•]. A total of 69 out of 75 suffered from AD. Of 209 oral challenges, 133 were performed with allergen and 76 with placebo. A total of 77 out of 133 allergen and two out of 76 placebo challenges were assessed as positive. In 66 out of 77 (86%) positive oral challenges specific IgE in serum to the corresponding allergen was positive; 64 out of 77 (83%) of the SPTs, and 42 out of 77 (55%) of the APTs were positive. Immediate-type clinical reactions were associated with positive SPT and proof of specific IgE in serum. Whereas the sensitivity of late-phase clinical reactions was 76% and specificity was 95%, corresponding figures for the SPT were 58 and 70%, and for the specific IgE in serum 71 and 29%, respectively [9•].

Majamaa *et al.* [14] and Vanto *et al.* [15] investigated the performance of allergological tests in suspected cows' milk allergy. In the first study [14], the APT was positive in 44% of cases of cows' milk allergy confirmed by challenge, APT was found to have a positive predictive value of 63% in the study, which is comparable to our positive predictive value of 70%. Similar to their findings, we found that the APT is the best predictor of positive challenges to cows' milk. Vanto *et al.* [15] investigated 301 children with suspected cows' milk allergy, and found a positive predictive value of 40% for the APT for immediate reactions, but no data could be provided for late-phase reactions. The authors concluded that APT results with cows' milk were not related to acute or delayed challenge reactions. Majamaa *et al.* [14] also investigated the usefulness of SPT, APT and specific IgE in 39 patients with wheat allergy, most of whom suffered from AD [16]. In their collective, 56% showed positive challenges, as in our patient group in which 51% reacted to wheat. With regard to the APT, these authors found a positive predictive value to wheat of 63% compared with 94% in our study.

In a recent study [17•], our group investigated whether the combination of the APT, SPT and specific IgE in serum could improve the diagnostic value. The APT was the best single predictive test (positive predictive value of 95%) for evaluating suspected cows' milk allergy, and the combination of a positive APT with evidence of specific IgE, or APT together with a positive SPT optimized the positive predictive value to 100%. Concerning hen's egg allergy, the APT was also the best single predictive test (positive predictive value of 94%). However, the combination of two or more tests did not exceed the predictive value of the APT. In both cows' milk and hen's egg challenges, the predictability of oral challenges depended on the level of specific IgE in serum. For wheat allergy, the APT proved to be the most reliable test and the positive predictive value of 94% could not be improved by combination with other allergological tests. Therefore, the combination of

Table 1. Assessment of the atopy patch test

Allergic reactions	Irritant reactions
Slow, crescendo	Rapid, decrescendo
Persistent	Short duration
Unsharp margin	Sharp margin
Marked erythema	Mild (brownish) erythema
Infiltration, papules	Bulla, necrosis

positive APTs together with defined levels of specific IgE (cows' milk ≥ 0.35 kU/l and hen's egg ≥ 17.5 kU/l) makes DBPCFC superfluous for suspected cows' milk and hen's egg allergy.

More recently we investigated whether the APT could discriminate between IgE-mediated ($n=99$) and non-IgE-mediated ($n=12$) positive, oral DBPCFCs [18]. The hypothesis was that the APT may be more often positive in the non-IgE-mediated group. However, this was not the case; neither the age of the children nor total IgE or the kind of clinical reaction (early/late) was significantly different between the two groups. Only the type of allergen showed a significant difference [18].

Open questions

Although the role of the APT in the diagnostic of food allergy has become much clearer during the last years, several questions remain to be answered in future studies.

Age of children

Age does not seem to have an influence on the outcome of the APT, which may be performed in infants as well as in older children [9•]. However, no results are available for the APT with foods in adults.

Atopic dermatitis

Patch test reactions to aeroallergens seem to be specific for sensitized AD patients, and are not found in healthy volunteers or in patients suffering from asthma or rhinitis [19]. In our study [9•], six out of 75 children did not suffer from AD and had no history of skin symptoms: none of these children showed a positive APT. However, the numbers involved are not sufficient to test whether the Dutch results in adults [19] are also valid for children with food-sensitive AD.

Allergens

In our studies, the APT was performed with native foods: cows' milk, hens' eggs, wheat and soy, which represent the four most common food allergens in childhood. Other studies have used similar food allergens [4,14–16]. All the findings indicate that native foods seem to be preferable to allergen extracts for performing APT, and the favourable results obtained in our studies may be due to the fact that we used identical fresh material for the SPT, APT and oral food challenges. There is no reason to doubt that many other allergens will also work. Unfortunately, no publications have appeared so far on peanuts.

Allergen concentration

As there is little information about the best concentration of food for the APT, and so as to exclude false-positive results by irritative reactions, all allergens were tested in parallel in a 1:10 solution [9•]. We observed 18 out of 77

(23%) positive results in the 10% diluted APT, and these were seen in the patients with the strongest reactions to the undiluted APT. Furthermore, all these patients showed late eczematous reactions in the DBPCFC, mostly to wheat ($n=10$) [9•]. This indicates that our APT results are not biased by unspecific, irritative reactions, and that undiluted native foods may be used.

Chamber size

Unpublished work from our group suggested that the use of 6 mm aluminium cups result in a markedly decreased sensitivity compared with the use of 12 mm aluminium cups, which we therefore prefer. There are no reports on the suitability of alternative materials such as rectangular plastic cups, now available on the market.

Reading time

For aeroallergens, studies have been performed comparing different reading times. It was concluded that an occlusion time of 48 h and a reading time of 72 h were preferable [20]. For food allergens, we know of no comparable studies. However, our group and others have obtained good predictions using a 48 h occlusion and 72 h reading time. One study [21] used a reading time of 96 h.

Modulation of anti-inflammatory skin treatment

Only one study [22•] has investigated the possible modulation of the APT by an anti-inflammatory skin treatment: glucocorticosteroids and tar were both able to reduce the macroscopic outcome of the APT reaction and the influx of inflammatory cells; however, all cell types remained present. The authors concluded that the APT could be used to evaluate the effect of topical anti-inflammatory treatments. The practical consequence is that the APT should be performed on non-treated skin.

Contact urticaria

Six children could not be evaluated in our studies because they showed clinically relevant reactions, with acute local urticarial wheals and itching (contact urticaria) 5–15 min after administering the APT [9•]. In these six cases, egg was the allergen. Otherwise, no side-effects were observed.

Evaluation of transience or persistence of food allergy

Unpublished first data from our group indicated that, although it is very helpful at the time of the first diagnosis, APT cannot predict whether a child will show a clinical reaction to the corresponding food after a period of avoidance. Therefore, oral re-challenges remain mandatory.

Sensitizing potential

No results are available for the potential sensitizing risk of the APT. For the SPT, there are no indications for a

sensitizing potential in the literature; however, the APT lesion may alter the barrier function of the skin, as was be shown by Gfesser *et al.* [23].

Conclusion

The APT seems to be a valuable additional tool in the diagnostic work-up of food allergy in infants and children with AD. A positive APT may help: (1) to detect clinically relevant late-phase eczematous reactions, leading to effective specific diets; and (2) to prevent restrictive and unnecessary diets, which may be the consequence of misjudging late reactions by clinical assessment alone. However, several open questions indicate the need for further studies.

The following statements may at present be justified regarding the role of the APT in the diagnostic work-up of food allergy in children:

- (1) A suspicion of food-related symptoms (history) should be the indication to perform oral food challenges, rather than the proof of specific IgE;
- (2) In addition to the specific IgE measurements (SPT or specific IgE in serum) and the history, the APT may be helpful in unclear or discrepant situations;
- (3) The APT has a definite role in assessing clinical late-phase reactions during oral provocations;
- (4) The combination of positive APTs together with defined levels of specific IgE makes DBPCFCs superfluous for suspected cows' milk and for hen's egg allergy in some cases;
- (5) In most cases, the ultimate test of food allergy is still the correctly performed DBPCFC.

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