REVIEW ARTICLE

ATOPY PATCH TEST IN THE DIAGNOSIS OF FOOD ALLERGY IN CHILDREN WITH ATOPIC DERMATITIS

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Summary: Atopic eczema/dermatitis syndrome (AEDS) is one of the most common chronic allergic diseases in children. Among the allergens found to be relevant in AEDS, aeroallergens and food allergens are the most important. The exposure of these patients to their relevant protein allergens can trigger an exacerbation or maintain the disease. AEDS is frequently associated with food allergy, which complicates the management in approximately 40% of these children. Atopy patch test (APT) can help in detecting food allergies in children with AEDS. The earliest publication on patch testing in eczema was described in 1937 by Rostenberg, but the first controlled clinical trial was provided by Mitchell in 1982. APT with food allergens were introduced into clinical use in 1996 by the group of Isolauri. APT test is performed epicutaneously with typical immediate-type allergens (aeroallergens or foods). As a number of apparently minor test modifications greatly influence the sensitivity, specificity, and reproducibility of the APT, the European Task Force on Atopic Dermatitis (ETFAD) has developed a standardized APT technique. APT has developed into a valuable additional tool in the diagnostic work-up of food allergy in infants and children with atopic dermatitis.

Key words: *Atopic eczema/dermatitis syndrome; Food allergy; Diagnosis; Atopy patch test; Children*

Atopic eczema/dermatitis syndrome (AEDS) is one of the most common chronic allergic diseases in children. It is characterized by recurrent intense pruritus and a typically age-related distribution and skin morphology (erythematous and pruritic lesions, excoriations, papules and lichenification), and affecting 10–20% of children, although the incidence is increasing (during the last 5 years it has increased twofold) (9). The prevalence among adults is about 1–3%. AEDS is multifactorial disease mediated by both intrinsic abnormalities (immunological and pharmacological) and extrinsic factors, such as food, airborne and contact allergens, and irritants (16). Among the allergens found to be relevant in AEDS, aeroallergens and food allergens are the most important (4). Food allergy has been demonstrated to play an important role in the pathogenesis of AEDS (relevant clinical hypersensitivity to food has been shown in 30–70% patients with mild to severe AEDS in double-blind, placebo-controlled oral food challenges) (3,7). Egg white, nuts, seafood and peanuts are the most frequently (80–90%) incriminated allergens; in children soy, cow's milk and wheat flour are also responsible. There is no specific marker for AEDS and the diagnosis is made by a combination of clinical features. Therapeutic consequences of diagnosis of an allergy are based upon avoidance strategies, which can be very expensive and distressing for the patient (4). 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 challenge, the evaluation of food allergy in the absence of immediate clinical reactions (worsening of eczema) still presents diagnostic difficulties – particularly in polysensitised children with AEDS (13). Skin prick testing, measurement of specific IgE and food challenges are helpful in the IgE-mediated reactions, but diagnosing patients who have the non-IgE (cell mediated) or mixed (IgE and cell mediated) disorders remains challenging with our current diagnostic tools (18). Oral provocation test remains the "gold standard" for the food allergy diagnosis. The provocation is performed as double-blind placebo-controlled food challenge (DBPCFC), e.g. with "masked" (lyophilized) foods in colour and flavour neutral formulas after at least 2 week of corresponding elimination diet. For AEDS, early (within 1–2 h after provocation) and late reactions (2–24 h) can be distinguished (4).

Atopy patch test (APT) seems to be a valuable additional diagnostic tool in the diagnostic work-up of food allergy in children with AEDS, especially with regard to late-positive clinical reactions. APT involves the epicutaneous application of intact protein allergens (1st type of allergen) in a diagnostic patch test setting with an evaluation of the induced eczematous skin lesions after 24 to 72 hours. The APT reaction is initiated by binding of allergens to epidermal IgE^+CD1a^+ cells, which present allergen to allergen-specific T_{H2} cells in the dermis. Subsequent release of T_{H2}-cell-

derived cytokines will lead to an inflammatory reaction in which among others skin-infiltrating eosinophils are involved (2). Biopsy specimens of the positive patch test sites in patients with AEDS were found to have initial T_{H2} cell infiltration, followed by a predominance of T_{H1} cytokines and eosinophils (4). Similar biopsy findings have been observed in the skin of atopic dermatitis patients during acute and chronic lesions (9). The close microscopic and macroscopic similarities between the specimens from APT sites and lesional skin of patients with AEDS indicate that the APT is a valid model to study allergic inflammation in AEDS (22).

Tab. 1: The European Task Force on Atopic Dermatitis (ETFAD) protocol for atopy patch testing (20).

The ETFAD protocol for APT
• Test area: uninvolved skin of upper back
• No tape-stripping, scalpel abrasion or pre-treatment (acetone...)
• Large Finn Chambers (12 mm) on Scanpor tape
• Purified allergen in petrolatum as test substance with standardized allergen concentration (in biologic units or µg/mL major allergen content)*
• Occlusion time of 48 hours
• Reading at 48 hours (20 minutes after removing of the set) and 72 hours
Exclusion criteria for APT: – test site free of topical steroids for 7 days – test site without ultraviolet treatment for 4 weeks – patients free of oral steroids, cyclosporine A or tacrolimus – avoidance of antihistamins for 5 days – non-pregnant
** Whereas the availability of standardized food allergens is poor and many foods contain more than one protein which can cause allergic reaction, fresh native foods or dried foods dissolved in saline or water can be used for APT (20).*

Tab. 2: Revised European Task Force on Atopic Dermatitis (ETFAD) key for atopy patch test reading (8, 20).

Key for atopy patch test reading		
–	negative	***negative***
?	only erythema, questionable	
+	erythema, infiltration	***positive***
++	erythema, few papules (< 3)	
+++	erythema, many or spreading papules (>4)	
++++	erythema, papules and vesicles	

Tab. 3: Distinguishing among allergic and irritant reactions (12).

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

As a number of apparently minor test modifications greatly influence the sensitivity, specificity, and reproducibility of the APT, the European Task Force on Atopic Dermatitis (ETFAD) has developed a standardized APT technique (Table 1), although some conditions still remain controversial especially the poor availability of standardized food allergen mixtures (the situation for aeroallergens is different, because the standardized testing material is already existing) (8). In literature we can find different methods of preparing the test materials and these differences among the authors cause controversial results (20). Most of authors recommend the use of native food allergens (e.g. fresh cow's milk containing 3.5% fat, native whisked hen's egg, wheat- powder dissolved in saline or water – 1 g/10 ml, soy milk), however, the main allergen concentration is not sure. Some standardization in food APT testing bring new so-called "Ready-to-use" APT with already integrated allergens of known, standardized concetration (Diallertest® and E-patch® for cow's milk, Rapid patch set® for 10 food allergens) (5,17). The use of fresh native food is advantageous, because then this testing material could be used also by skin prick testing or food challenges and the results of these three tests are better comparable (12). Until validation data are available, fresh foods should be preferred for testing over commercial extracts (20). In the future, we should expect the use of recombinant proteins (for some aeroallergens they are already existing, e.g. *Malassezia furfur*) (20). Most of the authors use aluminium chambers with diameter of 12 mm (Finn Chambers) placed on hypoallergenic tape (Scanpor Tape). There are only a few reports on the suitability of alternative materials such as rectangular plastic cups, now available on the market (12). The application site (uninvolved area of upper back), according to some authors, should be checked 15 minutes after the beginning of the testing for eventual presence of immediate skin reaction (12), although this is possible especially by using "Ready-to-use" APT with transparent membrane, which allows easy evaluation of eventual immediate response without removal of testing set. In other cases it is possible to remove the set and then re-stick it again on the back of tested subject.

The crucial moment in food APT testing is the "reading" of skin response what requires wide clinical experience with classic standard epicutaneous and also epicutaneous atopy patch tests (6). The APT should result in a clear "yes" or "no" answer. Positive reaction may be classified using + for erythema and infiltration, ++ for erythema and less than 3 papules, +++ for erythema and four or more or spreading papules, ++++ erythema, papules and vesicles (Table 2). Irritant reactions (sharply defined brownish erythema, decrescendo phenomenon, blistering, lack of clear infiltration) are not positive (Table 3). Erythema without palpable infiltration is considered as questionable, finally negative reaction (12) (Table 2).

Any food can be assessed with patch testing, but cow's milk, hen's egg, wheat and soy have been studied most extensively (12–14,18,19). Side effect are uncommon, although reports of contact urticaria in small number patients (13) or irritation reactions (10,11,21) have been reported. The combination of positive APT results together with defined levels of specific IgE makes DBPCFCs in some cases superfluous (14). APT helps to prevent unnecessary restrictive diets which may be the consequence of misjudging late reactions by clinical assessment alone (13).

According to our experience, APT is simple, cheap and informative diagnostic method, especially when determining delayed type of allergic reactions in children with suspected food allergy. We prefer the use of fresh food allergens or wheat dissolved in saline placed in rectangular plastic cups on hypoallergenic tape. This method could help in the assessment of suspected food before following oral exposure test.

APT with food allergens may increase the identification of food allergy in patients with ADES especially in these cases: suspicion of food allergy without predictive specific IgE levels or a positive skin prick tests; severe and/or persistent AEDS with trigger factors of unknown origin; multiple IgE sensitizations without proven clinical relevance in patients with AEDS (20). It is suitable to perform skin patch test among infants and pre-school children, when total IgE amount in blood is normal and skin prick test are negative (15). Food challenges are still necessary for the appropriate diagnosis of food allergy in patients with AEDS. 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 (13).

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