

## Original article

# Combined skin prick and patch testing enhances identification of peanut-allergic patients with atopic dermatitis

**Background:** Food atopy patch tests (APTs) are considered a useful tool for the diagnosis of food allergy. Hypersensitivity to peanuts has not been investigated by means of APTs so far.

**Methods:** APTs and skin prick tests (SPTs) with peanuts were performed in 136 atopic dermatitis (AD) patients. Relevance of positive and negative responses to these tests was assessed by repeated open challenges with peanuts.

**Results:** Nine percent of our AD patients reacted to the challenge. Positive responses to APTs were recorded in 19% of the patients, whereas in 12% positive SPTs were observed. APTs were more frequently positive in subjects with eczematous responses after challenge with respect to those with urticarial reactions. SPT reactivity proved to be higher in patients above 12 years of age, whereas APT positivity was more frequent in children under 6 years. APT sensitivity proved significantly higher than SPT sensitivity, in particular in children under 12 years of age. On the contrary, SPT specificity and positive predictive value were significantly higher with respect to those of APT in the age group of subjects under 6 years of age.

**Conclusions:** Our data suggest that APTs with peanuts may represent a useful integration to standard testing modalities employed for the diagnosis of peanut allergy in AD patients.

**S. Seidenari, F. Giusti, L. Bertoni, L. Mantovani**

Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy

Key words: atopic dermatitis; atopy patch tests; food challenge; peanut allergy; skin prick tests.

Stefania Seidenari  
Department of Dermatology  
Via del Pozzo  
Modena  
Italy

Accepted for publication 6 February 2003

Atopic dermatitis (AD) is a recurring inflammatory skin disorder, which is often associated to food allergy, especially in infants and children (1–3). The most frequently offending foods are cow's milk, egg, wheat, and soy, but other foodstuffs have been shown to exacerbate the dermatitis (2). Peanut allergy represents an increasing problem in Western countries, involving approximately one in 150–200 subjects (4–6). The mean age at detection is decreasing and also 2–3-year-old children are affected. Even a small amount of peanuts can elicit a reaction and the onset of symptoms is prompt in many cases (7). However, in our experience, in children with AD delayed reactions to peanuts can be observed.

Routine diagnostic work-up of suspected allergy to food in subjects with AD includes *in vivo* or *in vitro* detection of specific IgE by means of skin prick tests (SPTs) or serologic assays (8–11). However, the results of SPTs as predictors of allergen-mediated skin reactions are frequently disappointing, since their correlation to the appearance of delayed eczematous reactions may be poor. To date, a correct diagnosis of food allergy is based on the response to the elimination of the food from the diet, followed by the appearance of clinical symptoms after clinical exposure performed by a controlled food challenge (12–14). Recently, patch testing with food allergens

has been introduced as a procedure enabling the identification of AD patients reacting with a dermatitis to the administration of the offending food (15–21).

The aim of our study was to investigate prick and patch test responses to peanuts in subjects with AD, and to correlate their results to those of repeated open food challenges in these subjects.

## Material and methods

### Patients

One hundred and thirty-two patients affected by AD (53 males and 79 females), aged 3–28 years (mean age  $\pm$  SD =  $12 \pm 7$  years) were studied. AD was diagnosed according to the criteria of Hanifin and Rajka (22). Severity of eczema was evaluated according to the SCORAD score ranging from 0 to 103 points, with assessment of topography items (affected skin area), intensity criteria (erythema, edema, crusts, excoriations, lichenification, and xerosis), and subjective parameters (intensity of itch and loss of sleep) (23). Forty-four patients had mild AD (SCORAD < 25 points), 69 had moderate AD (SCORAD = 25–50 points), and 19 had severe AD (SCORAD > 50 points). No patients had been treated with systemic steroids, antihistamines with prolonged half-lives or cyclosporin for 4 months prior to the beginning of the study, and the administration of other drugs, including antihistamines, was

discontinued 7 days before patch testing. Only topical treatment with emollients and antibiotics was continued.

### Skin prick tests

SPTs were performed on the volar surface of the forearm, according to the standard technique, using commercial allergens from Stallergènes (Antony, France) and Lofarma (Milan, Italy). Reactions were read at 15–20 min, and the tests were assessed as positive if the wheal diameter was 3 mm or larger. A solution of histamine dihydrochloride (10 mg/ml) was used as a positive control.

### Atopy patch tests (APTs)

For the preparation of the patch test material, peanuts were whipped and a mixture was made with one part of petrolatum and two parts of peanuts. Twenty milligrams of this material were applied to the uninvolved skin of the back by using large (12 mm diameter) Finn chambers on Scanpor tape (Epitest, Tuusula, Finland). Filter paper within a Finn chamber was used as a negative control. The occlusion time of APTs was 72 h and the results were read 30–60 min after removal, according to the following scale: erythema and edema = 1; erythema, edema, and few papules = 2; erythema, edema, and papules covering most of the patch test area = 3; erythema, edema, and papules spreading outside the patch test area or vesicles = 4. Irritant or doubtful reactions included redness with no infiltration. For calculating sensitivity, specificity, positive and negative predictive values APT reactions graded as 1 were taken as negative.

### Specific IgE assays

Sera from 75 patients were analyzed for specific IgE antibody to peanuts by using the Pharmacia uniCAP System FEIA (Pharmacia, Uppsala, Sweden).

### Repeated open food challenge

Before challenge, the patients had been on a milk, egg, and peanut elimination diet for at least 4 weeks. After a successful elimination diet, as judged by the disappearance of most skin lesions, in patients without a history of severe adverse reactions to foods, a repeated open challenge with peanuts was performed according to the following modalities: peanuts were administered at the hospital the first day, and at home, the following days, in an increasing pre-established amount. The first day the patients were given six pieces of peeled peanuts and three pieces were added each day for the following 6 days up to a maximum dose of 24 pieces of peeled peanuts. When a clinical reaction (cutaneous, respiratory, or gastrointestinal) appeared, the challenge was discontinued and the patient immediately examined by the medical staff. Skin reactions were recorded and described as urticarial or eczematous. All patients were examined on day 7 of the challenge. In 12 cases, where the outcome of the challenge was not clear, the patient was once again put on a diet and the challenge was repeated after 2–4 weeks. Only the results of the second challenge were considered here.

Written informed consent was obtained from the patients entering the study or from their parents.

### Statistical methods

Statistical analyses were performed using a SPSS (release 10.0 for Windows, SPSS, Chicago, IL) software package. The chi-squared

test was used to check variations between frequencies of skin test reactions according to challenge outcome and to age. A *P* value <0.05 was considered statistically significant. Sensitivity, specificity, positive and negative predictive values, and overall agreement were calculated. Sensitivity is defined by the number of subjects with a positive challenge identified as correct by the test/total number of subjects with a positive challenge. Specificity is defined by the number of subjects with a negative challenge identified as correct by the test/total number of subjects with a negative challenge. The positive predictive value describes the proportion of symptomatic individuals among those with positive test results. The negative predictive value describes the number of nonsymptomatic individuals among those with negative test results. The overall agreement describes the proportion between the total number of subjects correctly classified by the test and the total number of subjects tested.

## Results

SPTs were positive in 16 patients (12%), whereas APTs proved positive in 25 (19%).

A positive challenge was observed in 12 subjects (9%). At the time of the challenge, the mean age of the subjects with a positive and a negative challenge was  $10.8 \pm 6.3$  and  $12.1 \pm 7.1$  years, respectively. SCORAD values were significantly higher in challenge-positive patients than in negative ones ( $46.8 \pm 10.0$  vs  $29.9 \pm 15.1$ ). Among challenge-positive patients, one showed an immediate urticarial reaction and reacted to SPTs alone (Fig. 1). Five subjects presented both immediate and delayed responses: among these, two reacted to SPTs and three to APTs. In six cases, only an eczematous response was observed, appearing 12–96 h after the first administration of peanuts. All of the latter were positive to peanut APTs, whereas one patient to SPTs alone. Extracutaneous symptoms included cough appearing immediately after ingestion of peanuts and gastrointestinal symptoms such as abdominal pain and diarrhea.

Figure 2 shows the results of SPTs and APTs with peanuts in both challenge-positive and -negative patients. Among 12 subjects reacting to the challenge, six proved

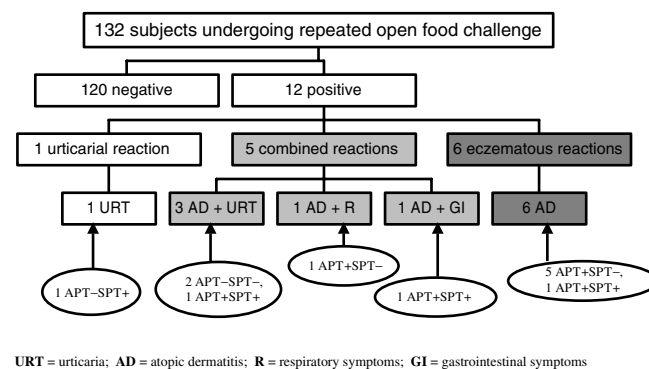


Figure 1. Outcomes of repeated open food challenge with peanuts in 132 AD patients.

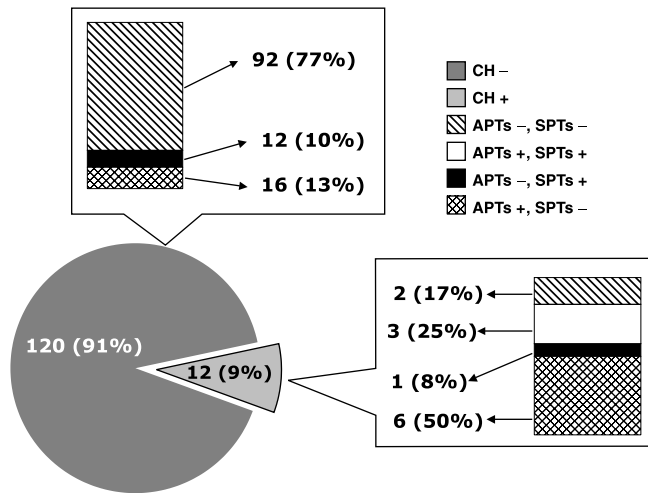


Figure 2. Results of skin tests with peanuts in 132 subjects undergoing challenge.

positive only to APTs, one to the SPT alone, three reacted to both skin tests, whereas two showed negative responses. Of 120 challenge-negative patients, 16 were positive only to APTs, 12 reacted to SPTs alone, whereas 92 proved negative. SCORAD values were significantly higher in subjects reacting to APTs and SPTs than in patients showing negative responses ( $39.9 \pm 11.0$  vs  $27.6 \pm 16.4$ ). In patients in whom total IgE levels were determined, the values differed neither between challenge-positive and -negative patients, nor between APT- and SPT-positive subjects.

The results of peanut challenge and skin tests in three different age groups are shown in Table 1. A positive challenge to peanuts was observed in 8–11.8% of our patients. The frequency of APT reactivity decreased in patients over 12 years of age (although not significantly), whereas SPT positivity was significantly higher in this age group in comparison with children under 6 years of age. Among the latter, SPT responses proved significantly less frequent than APT ones. Agreement between results of challenge and skin tests was 85.6 and 84.8% for APTs and SPTs, respectively.

Figures referring to sensitivity, specificity, positive and negative predictive values are given in Table 2. On the whole, APT sensitivity proved significantly higher than SPT sensitivity, in particular in children under 12 years of age. On the contrary, APT specificity and positive predictive value proved significantly lower with respect to those of SPT in the age group of subjects under 6 years of age. In the remaining age groups, APT positive predictive values were higher than SPT, in particular values in patients older than 12 years. APT sensitivity proved significantly higher in children under 6 years of age than in older subjects. As regards SPTs, positive predictive value decreased significantly in patients over 6 years of age, whereas in subjects older than 12 years sensitivity proved higher and specificity lower.

## Discussion

The frequency of allergy to peanuts is on the rise, although figures are probably underestimated since

Table 1. Results of challenge (CH) and skin tests with peanuts according to age

| Age group<br>(number of patients) | CH+ (%)  | APT+ (%)  | % Agreement<br>(APT and CH) | SPT+ (%)  | % Agreement<br>(SPT and CH) | % Agreement<br>(SPT and APT) |
|-----------------------------------|----------|-----------|-----------------------------|-----------|-----------------------------|------------------------------|
| <6 (48)                           | 4 (8.3)  | 12 (25)*  | 81.3                        | 2 (4.2)   | 91.7                        | 75                           |
| 6–12 (34)                         | 4 (11.8) | 8 (23.5)  | 82.4                        | 4 (11.8)  | 82.4                        | 68                           |
| >12 (50)                          | 4 (8)    | 5 (10)    | 90                          | 10 (20)†  | 94                          | 74                           |
| Total (132)                       | 12 (9.1) | 25 (18.9) | 85.6                        | 16 (12.1) | 84.8                        | 73                           |

\* Significant differences in comparison with SPTs.

† Significant differences in comparison with patients <6 years of age.

Table 2. Sensitivity, specificity, positive and negative predictive values of skin tests with peanuts according to age

| Age group<br>(number of patients) | APT<br>sensitivity (%) | APT<br>specificity (%) | APT positive<br>predictive<br>value (%) | APT negative<br>predictive<br>value (%) | SPT<br>sensitivity (%) | SPT<br>specificity (%) | SPT positive<br>predictive<br>value (%) | SPT negative<br>predictive<br>value (%) |
|-----------------------------------|------------------------|------------------------|-----------------------------------------|-----------------------------------------|------------------------|------------------------|-----------------------------------------|-----------------------------------------|
| <6 (48)                           | 100*                   | 81.8*                  | 25*                                     | 100                                     | 25                     | 97.7                   | 50                                      | 93.5                                    |
| 6–12 (34)                         | 75*†                   | 83.3                   | 37.5                                    | 96.2                                    | 25‡                    | 90                     | 25†                                     | 90                                      |
| >12 (50)                          | 50†                    | 93.5                   | 40*                                     | 95.5                                    | 50†                    | 82.6†                  | 20†                                     | 95                                      |
| Total (132)                       | 75*                    | 86.6                   | 36                                      | 97.2                                    | 33.3                   | 90                     | 25                                      | 93.1                                    |

\* Significant differences in comparison with SPTs.

† Significant differences in comparison with patients <6 years of age.

‡ Significant differences in comparison with patients >12 years of age.

peanuts may be contained in vegetable oils employed for baking products and pastries and are frequently ingested as hidden allergens (24). Besides SPTs and serum-specific IgE determination, elimination and challenge with the suspected food are indicated to reliably identify food allergic subjects. Although most authors consider the double blind placebo-controlled food challenge (DBPCFC) the gold standard for the diagnosis of food allergy also in AD patients, no general agreement on standardized protocols for performing the challenge test exists at present (12). Moreover, this test is time consuming, expensive, difficult to perform in young children, and bears the risk of severe allergic reactions. Finally, the classic procedure based on repeated administrations of the foodstuff for some hours and an observation period of 48 h does not fully mimic the repeated intake of food in a normal diet and may not identify the whole spectrum of skin reactions appearing in AD patients after food allergen exposure, which encompasses prompt and delayed responses sometimes requiring repeated administration. Isolauri and Turjanmaa performed both DBPCFCs (lasting 1 week) and repeated open food challenges with cow's milk in infants with AD and found a high correlation between these two testing modalities, detecting indistinguishable rates of positive reactions (15). Their data suggest that an open challenge with careful follow-up would be adequate for practical clinical purposes, also enabling the diagnosis of delayed reactions.

Repeated open food challenge with peanuts is easy to perform and child-friendly. In 12 of our patients, a positive challenge was observed. Among them, six urticarial reactions appearing shortly after the challenge and 11 eczematous responses appearing 12–96 h after the first administration of peanuts were recorded.

Some authors observed that on the basis of serum-specific IgE levels and the SPT wheal size it is possible to predict the challenge outcome in patients with peanut hypersensitivity remaining under observation for some hours (8–11). However, SPTs are not particularly suitable for disclosing eczematous reactions to dietary antigens. Laboratory tests such as assays on lymphocyte stimulation and cytokine generation have shown some promise in detecting delayed type reactions to food, but are not commonly available (25). Recently, APTs have been shown to be a useful diagnostic tool in suspected delayed reactions (15–21). Isolauri and Turjanmaa found that up to 50% of AD children allergic to cow's milk showed late-onset reactions to DBPCFC (15). This subgroup of AD patients was characterized by positive APTs (15) and by defective interferon (IFN)- $\gamma$  production *in vitro* (26). In the study by Majamaa et al., 44% of patients with challenge-proven cow's milk allergy showed positive APTs (17). In most of these patients reacting to APTs, SPTs with cow's milk were negative. Positive APTs for cow's milk proved highly associated with delayed type reactions to

challenge and were the more sensitive method to detect cow's milk allergy in this study population. However, 38% of the patients with a positive challenge to cow's milk did not react in skin testing or by RAST. Sütas et al. reported that in AD patients with food allergy oral challenge triggers systemic release of interleukin (IL)-10, and subjects with late-onset reactions have lower serum IL-10 concentrations than their immediate-reacting counterparts (27). Considering that IL-10 is an inhibitory cytokine of delayed type hypersensitivity, low IL-10 levels in late-reacting patients may explain their high frequency of positive APTs combined with negative SPTs.

According to our data, allergy to peanuts in AD patients is homogeneously distributed in all age groups. In fact, no variations were found in the frequency of positive challenges according to age. Subjects reacting to peanut challenge showed positive skin tests more frequently (75%) than challenge-negative patients (23%). Among challenge-positive subjects, six were identified by APTs alone, whereas only one by SPT alone, indicating that the APT procedure is more sensitive than SPT for the identification of AD patients with peanut allergy. This especially applies to children under 12 years of age, where figures for APT sensitivity ranged between 100 and 75% in comparison with a SPT sensitivity corresponding to 25%. As regards challenge-negative subjects, 77% showed negative skin tests, whereas only two out of 12 challenge-reacting patients proved negative to both SPTs and APTs. No significant variations were observable for SPT and APT specificity values according to age, except in children under 6 years. In our study population, positive APT reactions were more frequent in delayed responders: among 11 subjects showing combined or eczematous responses to challenge, nine had positive APTs to peanuts, whereas one patient alone reacted to SPT among six subjects with only eczematous responses.

During routine diagnostic work-up, our patients were prick tested with 66 food and inhalant allergens and 57% proved positive to at least one allergen. No significant difference in positivity figures to APTs with peanut were observed between SPT positive (extrinsic AD) and SPT negative (intrinsic AD) patients: (16 vs 23%).

To the best of our knowledge, no data on APTs with peanuts are available, so far. To date, the issue of peanut allergy in AD patients has only been investigated by means of SPTs and serologic assays. Our findings show that APTs are frequently positive (75%) in subjects with challenge-proven allergy to peanuts. Since SPT reactivity increases in patients above 12 years of age and APT positivity is more frequent in children under 6 years of age, APTs with peanuts may represent a useful integration to standard testing modalities employed for the identification of peanut allergic AD patients.

## References

- BURKS AW, JAMES JM, HIEGEL A, WILSON G, WHEELER JG, JONES SM, ZUERLEIN N. Atopic dermatitis and food hypersensitivity reactions. *J Pediatr* 1998;**132**:132–136.
- RANCÉ F, KANNY G, DUTAU G, MONERET-VAUTRIN DA. Food hypersensitivity in children: clinical aspects and distribution of allergens. *Pediatr Allergy Immunol* 1999;**10**:33–38.
- SCHÄFER T, BOHLER E, RUHDORFER S, WEIGL L, WESSNER D, HEINRICH J, FILIPIAK B, WICHMANN HE, RING J. Epidemiology of food allergy/food intolerance in adults: associations with other manifestations of atopy. *Allergy* 2001;**56**:1172–1179.
- RANCÉ F, DUTAU G. Peanut hypersensitivity in children. *Pediatr Pulm* 1999;**18**:165–167.
- PUCAR F, KAGAN R, LIM H, CLARKE AE. Peanut challenge: a retrospective study of 140 patients. *Clin Exp Allergy* 2000;**31**:40–46.
- SICHERER SH. Clinical update on peanut allergy. *Ann Allergy Asthma Immunol* 2002;**88**:350–361.
- HOURIHANE JOB, KILBURN SA, NORDLEE JA, HEFLE SL, TAYLOR SL, WARNER JO. An evaluation of the sensitivity of subjects with peanut allergy to very low doses of peanut protein: a randomized, double-blind, placebo-controlled food challenge study. *J Allergy Clin Immunol* 1997;**100**:596–600.
- SPORIK R, HILL DJ, HOSKING CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000;**30**:1540–1546.
- SAMPSON HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;**107**:891–896.
- HILL DJ, HOSKING CS, REYES-BENITO LV. Reducing the need for food allergen challenges in young children: a comparison of in vitro with in vivo tests. *Clin Exp Allergy* 2001;**31**:1031–1035.
- RANCÉ F, ABBAL M, LAUWERS-CANCÈS V. Improved screening for peanut allergy by the combined use of skin prick tests and specific IgE assays. *J Allergy Clin Immunol* 2002;**109**:1027–1033.
- BINDSLEV-JENSEN C. Standardization of double-blind, placebo-controlled food challenges. *Allergy* 2001;**56**:75–77.
- SAMPSON HA. Use of food-challenge tests in children. *Lancet* 2001;**358**:1832–1833.
- CAFFARELLI C, PETROCCIONE T. False-negative food challenges in children with suspected food allergy. *Lancet* 2001;**358**:1871–1872.
- ISOLAURI E, TURJANMAA K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996;**97**:9–15.
- KEKKI OM, TURJANMAA K, ISOLAURI E. Differences in skin-prick and patch-test reactivity are related to the heterogeneity of atopic eczema in infants. *Allergy* 1997;**52**:755–759.
- MAJAMAA H, MOISIO P, HOLM K, KAAUTIAINEN H, TURJANMAA K. Cow's milk allergy: diagnostic accuracy of skin prick and patch tests and specific IgE. *Allergy* 1999;**54**:346–351.
- VANTO T, JUNTUNEN-BACKMAN K, KALIMO K, KLEMOLA T, KOIVIKKO A, KOSKINEN P, SYVÄNEN P, VALOVIRTA E, VARJONEN E. The patch tests, skin prick test, and serum milk-specific IgE as diagnostic tools in cow's milk allergy in infants. *Allergy* 1999;**54**:837–842.
- NIGGEMANN B, REIBEL S, WAHN U. The atopy patch test (APT) – a useful tool for the diagnosis of food allergy in children with atopic dermatitis. *Allergy* 2000;**55**:281–285.
- SAARINEEN KM, SUOMALAINEN H, SAVILAHTI E. Diagnostic value of skin-prick and patch tests and serum eosinophil cationic protein and cow's milk-specific IgE in infants with cow's milk allergy. *Clin Exp Allergy* 2001;**31**:423–429.
- ROEHR CC, REIBEL S, ZIEGERT M et al. Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenge in children with atopic dermatitis. *J Allergy Clin Immunol* 2001;**103**:548–553.
- HANIFIN JM, RAJKA G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980;**92** (Suppl): 44–47.
- KUNZ B, ORANJE AP, LABREZE L, STALDER JF, RING J, TAIEB A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997;**195**:10–19.
- SCHÄPPI GF, KONRAD V, IMHOF D, ETTER R, WÜTRICH B. Hidden peanut allergens detected in various foods: findings and legal measures. *Allergy* 2001;**56**:1216–1220.
- RASANEN L, LEHTO M, REUNALA T. Diagnostic value of skin and laboratory tests in cow's milk allergy/intolerance. *Clin Exp Allergy* 1992;**22**:385–390.
- SÜTAS Y, HURME M, ISOLAURI E. Oral allergen challenge abolishes antigen-specific interferon- $\gamma$  production in the peripheral blood of children with atopic dermatitis and cow milk allergy. *Clin Exp Allergy* 1997;**27**:277–283.
- SÜTAS Y, KEKKI OM, ISOLAURI E. Late onset reactions to oral food challenge are linked to low serum interleukin-10 concentrations in patients with atopic dermatitis and food allergy. *Clin Exp Allergy* 2000;**30**:1121–1128.