

Original article

The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study

Background: The atopy patch test (APT) was proposed to evaluate IgE-mediated sensitizations in patients with atopic eczema (AE).

Objective: The prevalence and agreement with clinical history and specific IgE (sIgE) of positive APT reactions was investigated in six European countries using a standardized method.

Methods: A total of 314 patients with AE in remission were tested in 12 study centers on clinically uninvolved, non-abraded back skin with 200 index of reactivity (IR)/g of house dust mite *Dermatophagoides pteronyssinus*, cat dander, grass, and birch pollen allergen extracts with defined major allergen contents in petrolatum. Extracts of egg white, celery and wheat flour with defined protein content were also patch tested. APT values were evaluated at 24, 48, and 72 h according to the European Task Force on Atopic Dermatitis (ETFAD) guidelines. In addition, skin-prick test (SPT) and sIgE and a detailed history on allergen-induced eczema flares were obtained.

Results: Previous eczema flares, after contact with specific allergens, were reported in 1% (celery) to 34% (*D. pteronyssinus*) of patients. The frequency of clear-cut positive APT reactions ranged from 39% with *D. pteronyssinus* to 9% with celery. All ETFAD intensities occurred after 48 and 72 h. Positive SPT (16–57%) and elevated sIgE (19–59%) results were more frequent. Clear-cut positive APT with all SPT and sIgE testing negative was seen in 7% of the patients, whereas a positive APT without SPT or sIgE for the respective allergen was seen in 17% of the patients. APT, SPT and sIgE results showed significant agreement with history for grass pollen and egg white (two-sided $P > |Z| \leq 0.01$). In addition, SPT and sIgE showed significant agreement with history for the other aeroallergens. With regard to clinical history, the APT had a higher specificity (64–91% depending on the allergen) than SPT (50–85%) or sIgE (52–85%). Positive APT were associated with longer duration of eczema flares and showed regional differences. In 10 non-atopic controls, no positive APT reaction was seen.

Conclusion: Aeroallergens and food allergens are able to elicit eczematous skin reactions after epicutaneous application. As no gold standard for aeroallergen provocation in AE exists, the relevance of aeroallergens for AE flares may be evaluated by APT in addition to SPT and sIgE. The data may contribute to the international standardization of the APT.

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Key words: aeroallergens; atopic eczema; atopy patch test; European multicenter.

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Accepted for publication 8 March 2004

Atopic eczema [atopic dermatitis (AE)] is an inflammatory, chronically relapsing, non-contagious and extremely pruritic skin disease. Atopic sensitization with increased total and specific immunoglobulin E (sIgE) levels is a common finding in patients suffering from AE [for review, see Ref. (1, 2)]. Although the role of allergy in AE is still controversial, some patients with atopic eczema suffer from exacerbation of skin lesions after contact with or inhalation of aeroallergens, e.g. house dust mite (*Dermatophagoides pteronyssinus*), pollen, animal dander or after ingestion of allergy-inducing foods and improve after appropriate avoidance strategies (3, 4). It has been repeatedly shown that in certain patients, eczematous skin lesions can be induced by epicutaneous application of aeroallergens, e.g. house dust mite [for review, see Ref. (5, 6)]. This test procedure, an epicutaneous patch test using allergens known to induce IgE-mediated sensitizations and the evaluation of an eczematous skin reaction, is called 'atopy patch test' (APT) (7). Studies describing experimental patch testing with aeroallergens were published as early as 1937 by Rostenberg and Sulzberger (8) and in 1982 by Mitchell et al. (9); the methods and results used since then have shown wide variations. Potentially irritating procedures like skin abrasion (10, 11), tape stripping (6, 12) and sodium lauryl sulphate application (13) were used to enhance allergen penetration.

For better standardization, we performed APT on non-lesional, non-abraded, untreated skin during remission (7, 14). The results were compared for the vehicle and dose of allergen in the preparations used. It was shown that healthy controls and patients with respiratory atopy without a history of eczema do not react to the APT (14) or with a lower frequency and intensity of APT reactions to whole-body mite extract compared with patients with AE (15). Sensitivity and specificity of different diagnostic procedures were calculated in a previous multicenter study (16). Here, we present the results of a prospective European multicenter trial with biologically standardized APT preparations and corresponding allergy diagnosis in 314 patients with AE. This study was designed to define appropriate APT methods, safety aspects and relationship to clinical history of eczema flares using the most common allergens known to elicit reactions in AE patients in Europe. Another aim of the study was to determine the number of individuals with positive APT reactions, but negative sIgE (formerly diagnosed as 'intrinsic-type AE') in a larger patient group and to see whether the patients' history to a certain allergen is in agreement with the APT reaction, thus suggesting an important diagnostic role of the APT.

Methods

Patients

After approval by the local ethics committees and obtaining informed, written consent, 314 patients [age range 1.6–80 years; 177 female: mean age 22.6 ± 14.3 years (median 22.09); 137 male: mean age 22.9 ± 17.3 years (median 21.63)] with atopic eczema (1, 2) in actual remission, i.e. in a stable phase without acute flares of eczema, were enrolled in 12 study centers. The group included 76 (24%) children (≤ 10 years). There was no previous selection of patients for prior APT reactivity. Using the same standardized documentation forms for test results and clinical history in all study centers, all patients were examined for distribution of (residual) eczematous skin lesions and their history was recorded with regard to atopic diseases, AE duration, previous exacerbations (documentation in forms with regard to every single allergen tested, e.g. for seasonal eczema flares in previous years), previous location of eczema and demographic items. Mean duration of AE was 5.8 ± 5.5 years; 59% had a history of allergic rhinoconjunctivitis, 35% bronchial asthma and 23% urticaria. Before testing, patients were asked whether they experienced eczema flares and itching after contact with house dust or cat. Repeated seasonal variations of eczema severity or sudden, recurrent flares during the birch or grass pollen season (April/May and June to August) were also recorded. In addition, history comprised questions on eczema flares after ingestion of foods with special regard to egg, wheat and celery. 10 healthy, non-atopic volunteers (mean age 26.5 ± 1.2 years, five females) without positive skin-prick test (SPT) or elevated sIgE levels or other signs of atopy were included as controls.

Materials, atopy patch test design and reading

Aeroallergen APT were performed with extracts containing 200 index of reactivity (IR)/g of house dust mite *D. pteronyssinus*, cat dander, grass and birch pollen allergens in a petrolatum vehicle (Stallergènes, Antony, France). The potency of 100 IR was designated as the strength of allergenic extract that elicited a geometric mean wheal diameter of 7 mm on SPT in 30 subjects sensitive to the corresponding allergen. Major allergen contents (only available for aeroallergens) are given in Table 1. Extracts of egg white, wheat flour and celery were tested and standardized for protein content in petrolatum and protein contents are also shown in Table 1. After discontinuation of antihistamines, and systemic and topical steroids for at least 5 days, the test substances were applied in a randomized, double-blind design for 48 h in Large Finn Chambers (diameter 12 mm; Epitest Ltd, Oy, Finland) on clinically uninvolved, not pretreated back skin. All reactions were evaluated after 24 (reapplied), 48 and 72 h and compared with simultaneously performed corresponding SPT (Stallergènes), and specific sIgE [CAP-radioallergosorbent test (RAST)-fluorescence enzyme immunoassay; Pharmacia, Uppsala, Sweden] as classical methods for diagnosing type I sensitizations. Grading of positive APT reactions was similar to the criteria used in conventional contact allergy patch testing [International Contact Dermatitis Research Group (ICDRG) rules] with the modifications of the European Task Force on Atopic Dermatitis (ETFAD) Consensus Meetings (17); i.e. –, negative result; ?, only erythema, questionable; +, erythema, infiltration; ++, erythema, few papules (up to 3); +++, erythema, papules from 4 to < many; +++++, erythema, many or spreading papules; ++++++, erythema, vesicles. A patch test with the pure vehicle served as negative control. All investigators participated in pre-study standardized test reading sessions. Test application and reading were performed by different investigators. Thus, reading of reactions was performed by an investigator without the knowledge of

Abbreviations: AE, atopic eczema; APT, atopy patch test; ETFAD, European Task Force on Atopic Dermatitis; IDEC, inflammatory dendritic epidermal cell; IR/g, index of reactivity per gram; RAST, radioallergosorbent test; sIgE, specific serum immunoglobulin E; SPT, skin prick test.

Table 1. APT material: allergen and total protein content

Major allergen concentrations in the extracts (200 IR/g) (μg/ml) (ELISA)	
House dust mite	
Der p 1	59
Der p 2	6
Cat dander	
Fel d 1	9
Grass pollen	
Phl p 1	2
Birch pollen	
Bet v 1	165
Protein concentrations (μg/ml) (Bradford Method)	
House dust mite	98
Cat dander	75
Grass pollen	132
Birch pollen	334
Wheat	158
Celery	44
Egg white	740

Vehicle: petrolatum.

For food patch test preparations, only standardized protein content was available.

the (control) test sites or patient's history. Only reactions from + (i.e. erythema, infiltration) onwards were designated clear-cut positive.

The APT procedure in this study was performed in the same way as in our previous studies on AE patients and healthy controls (14, 16).

Statistics

Statistical analysis of the data was performed with SPSS®-Software using chi-square and linear association tests. After checking for normal distribution, paired *t*-test was used to compare mean rates of positive APT reactions, SPT and elevated sIgE in the study centers. Multivariate analysis was performed using a logistic regression model of APT outcome predictors.

Results

Patients' history of exacerbation after allergen contact/ingestion

10–39% of the patients reported eczema exacerbations after aeroallergen contact, mostly to house dust mite. Seasonal flares were reported in 17%. Food allergens were suspected in 1–7% of this mostly adult population. Table 2 shows the history in comparison with other clinical variables.

Eczema pattern

A total of 113 of the 314 patients (37%) reported skin lesions only in areas not covered by clothing and therefore a predictive eczema pattern for aeroallergen contact: the neck, face and scalp, hands and arms (over the last 12 months).

Skin-prick test and specific IgE

The frequencies of positive test results are given in Table 2. Concerning one allergen, the frequencies of SPT

Table 2. Positive test results and patients' history of allergen-associated eczema flare

Allergen	SPT	sIgE	APT	History	Concordance
<i>Dermatophagoides pteronyssinus</i>	56	56	39	34	57
Birch pollen	49	53	17	20	61
Grass pollen	57	59	15	31	64
Cat dander	44	46	10	30	62
Egg white	25	19	11	7	77
Wheat flour	16	38	10	3	78
Celery	20	30	9	1	79

All values are percentage values.

Frequency of positive APT reactions is lower than that of positive IgE-mediated sensitizations. Patients' allergen-specific history of eczema flares after allergen exposure was obtained prospectively. Concordance refers to APT and history. *n* = 314, 24% children ≤ 10 years.

SPT, skin prick test ≥ 3 mm; sIgE, specific IgE ≥ 0.35 kU/l; APT, atopy patch test ≥ +.

and sIgE, the classical tests of IgE-mediated hypersensitivity, were very similar to each other (except for wheat flour) and always higher compared with the frequency of a predictive history or positive APT. SPT reactions with a wheal diameter < 3 mm were regarded as negative.

Atopy patch test

All tested allergen preparations were able to elicit positive, clear-cut eczematous reactions in subgroups of patients, but not in control subjects. Positive reaction to the vehicle control area was only seen in three of 302 patients (0.99%). The frequency of the positive APT reactions is also given in Table 2. Whereas food allergens elicited positive reactions in the investigated population in about 10%, the most frequent allergen causing positive APT was *D. pteronyssinus* (39%), followed by pollen allergens. An example of a positive APT reaction is shown in Fig. 1.

Higher frequencies of positive APT reactions to food allergens were seen in children compared with adults (wheat flour: 15% vs 8%; celery: 12% vs 8%) except for egg white (both 11%).

The reactions to *D. pteronyssinus* are given in Fig. 2 with regard to their frequency at different timepoints and their intensity distribution. The results of other allergens are distributed similarly (not shown). Figure 2 also demonstrates, as an example, that at 24 h after application, only very few positive reactions were seen. Evaluations of APT after 48 and 72 h gave more frequently clear-cut positive reactions than after 24 h. Using the differentiated reading key of the ETFAD, the intensity of positive APT reactions is distributed similar to a log-arithmetic normal distribution.

Agreement analysis: history, skin prick test, specific IgE, eczema pattern

For grass pollen and egg white, APT, SPT and sIgE results showed significant concordance with a



Figure 1. APT reactions to different allergens after removal of Finn Chambers after 48 h. Clear-cut eczematous appearance with infiltration and spreading papules, partially with a follicular pattern. Control: petrolatum.

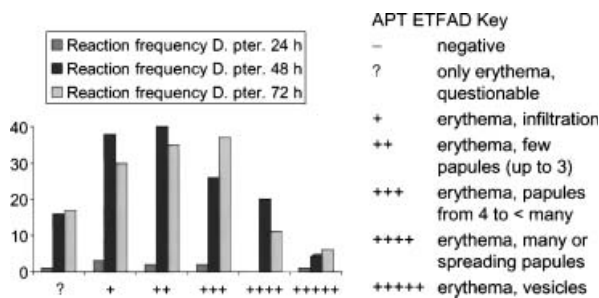


Figure 2. APT ETFAD grading: reaction frequencies of different intensities and timepoints. Distribution of patients with different APT reading key units according to ETFAD Consensus Meetings (17) for the most frequent allergen, house dust mite *D. pteronyssinus*. After 24 h, positive APT reactions were rare. APT reading after 48 and 72 h is recommended ($n = 314$).

prospectively obtained predictive history of eczema exacerbations (two-sided $\text{Pr} > |Z| \leq 0.01$). In addition, SPT and sIgE showed significant agreement with history for the other aeroallergens. In 83% of patients, corresponding SPT or sIgE results were found to match with the individual positive APT. A subgroup of patients was characterized by negative SPT and sIgE, but clear-cut positive APT results. There were 22 patients (7%) with clear-cut positive APT but without any positive SPT or elevated sIgE to all the allergens in the panel. With regard to a single APT-positive allergen, this was seen in 53

- Observed in 53 of 314 patients (17%)
- $N = 22$ APT+, but no positive SPT or sIgE at all (7%)

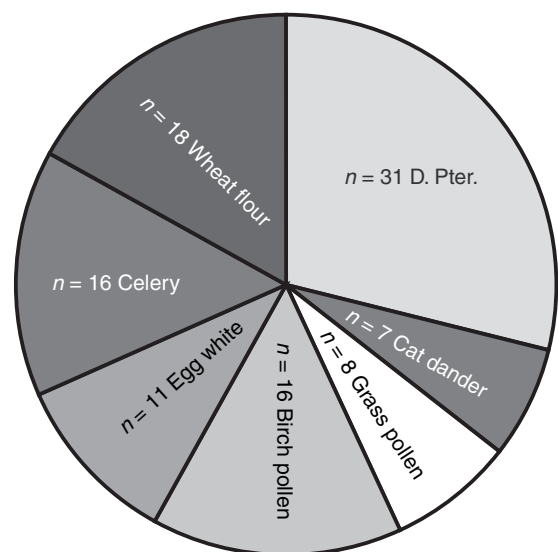


Figure 3. Patient subgroup with at least one positive APT reaction without corresponding skin-prick test/specific IgE. Clear-cut positive APT with all SPT and sIgE tested negative was seen in 7% of the patients, whereas a positive APT without SPT or sIgE for the respective allergen was seen in 17% of the patients.

Table 3. Sensitivity and specificity of different test procedures with regard to patients' history

Test	Sensitivity			Specificity		
	SPT	slgE	APT	SPT	slgE	APT
<i>Dermatophagoides pteronyssinus</i>	68*	72*	45	50*	53*	64
Cat dander	79*	80*	14	71*	69*	91
Grass pollen	80*	84*	28*	54*	53*	91*
Birch pollen	69*	73*	15	57*	52*	83
Egg white	68*	59*	32*	78*	85*	91*
Celery	100*	50	33	81*	71	91
Wheat flour	30	78	30	85	63*	91

All values are percentage values.
Referring to predictive history of eczema exacerbations in pollen season, in direct contact with allergen, or after food ingestion ($n = 314$).
* Agreement with history (two-sided $Pr > |Z| \leq 0.01$).
The APT shows a higher specificity than classical tests for IgE-mediated hypersensitivity with regard to the allergen-specific history.

(17%) of the patients. No significant difference in the agreement with history was seen when comparing these patients with the IgE-positive group. The distribution of allergens is shown in Fig. 3.

No significant association between air-exposed eczema distribution pattern and a positive APT result was seen ($P > 0.05$, $n = 188$). The duration of the last eczema flare in patients with at least one allergen with positive APT reaction ($n = 84$) was 186 ± 380 days (median 105 days). In patients with negative APT ($n = 104$), the duration was shorter: 143 ± 278 days (median 82 days; difference not significant, $P > 0.05$).

Sensitivity and specificity of different test procedures

The accuracy parameters sensitivity and specificity were calculated for all allergens and compared with the classic tests of IgE-mediated hypersensitivity (Table 3). The criteria for a 'true positive' test was, as usual in epicutaneous testing, a corresponding predictive history of the patient with the investigated allergen. It could be demonstrated in all tested allergens, that the specificity of the APT was always higher than the specificity of SPT or RAST. However, the sensitivity was lower, depending on the allergen studied.

Regional differences of APT reactivity

Table 4 shows the mean percentages of patients with positive APT reactions to the four tested aeroallergens, in comparison with different countries. Marked differences were seen in these numbers, especially for the seasonal pollen allergens and for cat dander. Less positive reactions to pollen were obtained in Switzerland, France and Italy compared with the Netherlands, Belgium and Germany. No significant regional differences were observed for food allergens (not shown). Comparing the percentual frequencies of positive APT and correspond-

Table 4. Percentage of positive APT per allergen and country

Country	Allergen			
	<i>Dermatophagoides pteronyssinus</i>	Cat*	GP*	BP*
The Netherlands ($n = 36$, 2 centers)	42	3	16	22
Belgium ($n = 32$, 2 centers)	44	13	8	19
Germany ($n = 162$, 4 centers) ¹	36	11	20	21
Switzerland ($n = 42$, 2 centers)	40	5	5	2
France ($n = 9$, 1 center) ²	67	11	0	11
Italy ($n = 30$, 1 center)	17	10	7	7

All values are percentage values.
Regional differences of APT reactions were seen.
¹ Including German Clinic in Davos, Switzerland.
² Pediatric study center.
* Association of APT with specific IgE, $P < 0.05$

ing elevated allergen-specific serum IgE per center, a paired t -test analysis showed significant association of these parameters for cat, grass and birch pollen.

Adverse events

In 25 of 314 patients (7.7%), adverse side-effects were reported, described as local eczema flares, contact urticaria, irritation caused by adhesives, and itching in test sites, some of which required topical therapy. One event was graded as severe, where a patient developed breathing problems in the night following APT and SPT. After removing of the APT and a lung X-ray, the patient recovered. A causal relation to the APT was unlikely.

Discussion

This is the first international multicenter study describing the feasibility of APT in a clinical setting with a controlled, double-blind design. The results of this study confirm that aeroallergens and food allergens are able to elicit eczematous skin lesions in a number of patients with atopic eczema when applied epicutaneously on untreated skin. The methodology used, in contrast to many experimental models for APT, is suitable for allergological routine, can be standardized across many sites, and can be interpreted on a clinical background in patients with atopic eczema.

As a 'gold standard' of aeroallergen provocation test in atopic eczema does not exist, the individual allergen-specific history of previous eczema exacerbations was used like in conventional contact allergy testing as a substitute for a relevance parameter. For aeroallergens, patient's history has previously been shown to be suitable to evaluate clinical relevance, especially for seasonal allergens (16, 17). Food provocation challenges were not included as no international standardization was achieved *a priori* and feasibility is large-scaled. In this study, significant associations of APT results with the prospec-

tively obtained history were seen with exposure to grass pollen as seasonal allergen and egg white as most frequent food allergen.

Atopy patch test evaluation after 48 and 72 h gave the number of positive APT results; however, after 24 h no relevant results could be obtained. The two later reading timepoints should be considered relevant in patch testing with aeroallergens; Fig. 2 shows a 10% higher frequency at 48 h compared with 72 h, for most positive APT key units. In addition, the distribution of APT reading key units in this multicenter study indicates the suitability of the ETFAD key for clinical routine. The cutoff of a positive APT reaction needing to be at least infiltrated (not only erythema) has previously been used successfully (14, 16); a visual score was recently shown to be superior in differentiation between irritative and allergic reactions compared with chromametry and laser Doppler imaging (18).

The sensitivity analysis, in comparison with previous studies (16, 17), suggests that for some allergens APT allergen concentrations >200 IR/g may be necessary to demonstrate a sensitization. Further studies with larger numbers of (pediatric) patients and including food challenges are necessary for food allergens, after better standardization of the allergen content. Celery was included as a known cross-allergen in adults (age >10 years in 76% of the study group) and indeed the number of patients with a positive APT to celery is markedly higher than the number of patients with a history of celery-associated eczema flares (Table 2). As a result of the overall low reactivity to celery APT and the lack of food provocation, these associations should be interpreted cautiously. Milk as a relevant food allergen in children could not be produced in a standardized APT preparation for this study. Higher numbers for sensitivity and specificity of APT with unprocessed native food were reported by Niggemann et al. (19) and Roehr et al. (20), using food provocation outcomes as calculation basis.

The regional subgroup analysis of this international multicenter study showed wide variations in the rate of positive APT reactions in spite of the highly standardized test procedure. This observation may partially explain the different outcomes of previous APT studies from different countries. Differences in patients' sensitization rates, probably due to different allergen exposure to certain aeroallergens may be one reason for this variation. This hypothesis is sustained by the significant association of the APT positivity rate and the corresponding specific IgE in the centers, arguing against investigator bias in APT reading (which was also standardized in training sessions).

The association of positive APT with specific IgE to certain allergens in this study suggests the role of allergen-specific IgE in the development of eczematous skin lesions after allergen contact in this study and confirms previous results (16). Mite allergen in the epidermis under natural conditions (21) as well as in APT sites (10, 13) has

been demonstrated in proximity to Langerhans cells. Langerhans cells in the skin express IgE receptors of three different classes (22–24). In addition, a Birbeck granule negative, non-Langerhans cell population with an even higher IgE-receptor expression than the Langerhans cell, the so-called inflammatory dendritic epidermal cell (IDEC), has recently been demonstrated in freshly induced APT lesions (25, 26), a phenomenon which occurred in both 'intrinsic' and 'extrinsic' patients (26). This might explain IgE-associated activation of allergen-specific T cells finally leading to eczematous skin lesions in the APT (27, 28). According to the results of Langeveld-Wildschut et al. (29) the positive APT reaction requires the presence of epidermal IgE⁺ CD1a⁺ cells.

That classical IgE-mediated tests like SPT and the proof of sIgE by CAP-RAST show positive reactions in the majority of patients with AE (1, 5, 14, 18), could also be demonstrated in this study. However, these tests are of low specificity. In contrast, the APT was associated with the more specific information, which patient really experienced deterioration of AE after aeroallergen contact. Therefore, the outcome of APT can only partially be predicted by sIgE, SPT or history, which, alone or in combination, can only be a substitute for the specific provocation or allergen avoidance measures. The very low frequency of reactions to vehicle control tests and the high number of positive reactions to allergen-carrying test substances in this study demonstrates the advantage of an APT method without irritating procedures like tape stripping or abrading to enhance allergen penetration.

In some patients with negative SPT with or without sIgE, clear-cut positive APT reactions were observed. It is well known that SPT and sIgE are not perfectly concordant when compared in a larger group of patients, since they may indicate sensitization in different compartments of the body (i.e. IgE on skin mast cells or in the serum). In contrast to SPT and sIgE, the APT gives additional information on another pathophysiological aspect, eczematous skin inflammation.

In summary, APT is not proposed as a single screening test in patients with atopic eczema. It may rather be used in addition to SPT and sIgE as a tool to prove clinical relevance of a given sensitization. A sensitization detected by APT, which is supposedly T-cell mediated, may be even more relevant for the clinical course of atopic eczema than the demonstration of an IgE-mediated sensitization. However, without the clear-cut positive APT, 7% of the tested patients who would be labelled as 'intrinsic type' of atopic eczema according to Wüthrich's definition (30), show a sensitization in the APT. A similar finding of positive APT reactions in subjects without sIgE to *Dermatophagoides* was described by Seidenari et al. (31) and Manzini et al. (32). Moreover, recently eight of 12 'intrinsic' atopic eczema patients were reported to react to a partially purified whole-mite APT preparation by Ingordo et al. (33). Similar results have been obtained by APT with *Malassezia sympodialis* antigen (34). House

dust mite-specific antibodies of the IgG4 subtype, as well as a rapid influx of IDEC in the APT lesions has recently been reported in two otherwise 'intrinsic' atopic eczema patients (35). However, the mechanism of these 'intrinsic' APT reactions remains hypothetical to date, but a T-cell-mediated mechanism without IgE involvement seems probable. With regard to the recently proposed novel nomenclature for allergy by the European Academy of Allergy and Clinical Immunology (36), these cases may be diagnosed as 'non-IgE-associated AEDS' or 'T-cell-mediated AEDS', respectively.

The APT model used in this study with standardization of allergen concentration and vehicle may provide an important diagnostic tool to select those patients who show special benefit from allergen avoidance procedures or allergen-specific immunotherapy (37). To date, there are no data from intervention studies supporting that

patients with positive APT benefit from allergen avoidance (38, 39). The APT with allergens in petrolatum may be used in the future as a kind of provocation test on the skin, but food challenge tests as gold standard in food allergic patients with AE are not replaced. The APT may even identify those patients with negative SPT and sIgE. However, the clinical relevance of positive APT reactions is still to be proven by standardized provocation and avoidance tests and may also depend on the APT model used and outcome definitions.

Acknowledgments

The authors are thankful to J. Grosh for skillful technical assistance and to the Technical University Munich for funding.

References

1. RAJKA G. Essential Aspects of Atopic Dermatitis. Berlin: Springer, 1989.
2. RUZICKA T, RING J, PRZYBILLA B., eds. Handbook of Atopic Eczema. Berlin: Springer, 1991.
3. TAN B, WEALD D, STRICKLAND I, FRIEDMAN P. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996;**347**:15–18.
4. TUPKER R, DEMONCHY J, COENRAADS P, HOMAN A, VAN DER MEER J. Induction of atopic dermatitis by inhalation of house dust mite. *J Allergy Clin Immunol* 1996;**97**:1064–1070.
5. RING J, DARSOW U, ABECK D. The atopy patch test as a method of studying aeroallergens as triggering factors of atopic eczema. *Dermatol Treatment* 1996;**1**:51–60.
6. VAN VOORST VADER PC, LIER JG, WOEST TE, COENRAADS PJ, NATER JP. Patch tests with house dust mite antigens in atopic dermatitis patients: methodological problems. *Acta Derm Venereol* (Stockh) 1991;**71**:301–305.
7. RING J, KUNZ B, BIEBER T, VIELUF D, PRZYBILLA B. The 'atopy patch test' with aeroallergens in atopic eczema. *J Allergy Clin Immunol* 1989;**82**:195.
8. ROSTENBERG A, SULZBERGER MD. Some results of patch tests. *Arch Dermatol* 1937;**35**:433–454.
9. MITCHELL E, CHAPMAN M, POPE F, CROW J, JOUHAL S, PLATTS-MILLS T. Basophils in allergen-induced patch test sites in atopic dermatitis. *Lancet* 1982;**i**:127–130.
10. GONDO A, SAEKI N, TOKUDA Y. Challenge reactions in atopic dermatitis after percutaneous entry of mite antigen. *Br J Dermatol* 1986;**115**:485–493.
11. NORRIS P, SCHOFIELD O, CAMP R. A study of the role of house dust mite in atopic dermatitis. *Br J Dermatol* 1988;**118**:435–440.
12. BRUIJNZEEL-KOOMEN C, VAN WICHEN D, SPRY C, VENGE P, BRUIJNZEEL P. Active participation of eosinophils in patch test reactions to inhalant allergens in patients with atopic dermatitis. *Br J Dermatol* 1988;**118**:229–238.
13. TANAKA Y, ANAN S, YOSHIDA H. Immunohistochemical studies in mite antigen-induced patch test sites in atopic dermatitis. *J Derm Science* 1990;**1**:361–368.
14. DARSOW U, VIELUF D, RING J. Atopy patch test with different vehicles and allergen concentrations – an approach to standardization. *J Allergy Clin Immunol* 1995;**95**:677–684.
15. SEIDENARI S, GIUSTI F, PELLACANI G, BERTONI L. Frequency and intensity of responses to mite patch tests are lower in non atopic subjects in respect to patients with atopic dermatitis. *Allergy* 2003;**58**:426–429.
16. DARSOW U, VIELUF D, RING J, for the APT Study Group. Evaluating the relevance of aeroallergen sensitization in atopic eczema with the atopy patch test: a randomized, double-blind multicenter study. *J Am Acad Dermatol* 1999;**40**:187–193.
17. DARSOW U, RING J. Airborne and dietary allergens in atopic eczema: a comprehensive review of diagnostic tests. *Clin Exp Dermatol* 2000;**25**:544–551.
18. HEINEMANN C, SCHLIEMANN-WILLERS S, KELTERER D, METZNER U, KLUGE K, WIGGER-ALBERTI W et al. The atopy patch test – reproducibility and comparison of different evaluation methods. *Allergy* 2002;**57**:641–645.
19. NIGGEMANN B, REIBEL S, WAHN U. The atopy patch test – a useful tool for the diagnosis of food allergy in children with atopic edermatitis. *Allergy* 2000;**55**:281–285.
20. ROEHR CC, REIBEL S, ZIEGERT M, SOMMERFELD C, WAHN U, NIGGEMANN B. Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2001;**107**:548–553.
21. MAEDA K, YAMAMOTO K, TANAKA Y, ANAN S, YOSHIDA H. House dust mite (HDM) antigen in naturally occurring lesions of atopic dermatitis (AD): The relationship between HDM antigen in the skin and HDM antigen-specific IgE antibody. *J Derm Sci* 1992;**3**:73–77.
22. BIEBER T, RIEGER A, NEUCHRIST C, PRINZ JC, RIEBER EP, BOLTZ-NITULESCU G et al. Induction of FcεR2/CD23 on human epidermal Langerhans-Cells by human recombinant IL4 and IFN. *J Exp Med* 1989;**170**:309–314.
23. BIEBER T, DE LA SALLE H, WOLLENBERG A, HAKIMI J, CHIZZONITE R, RING J et al. Human epidermal Langerhans cells express the high affinity receptor for immunoglobulin E (Fc epsilon RI). *J Exp Med* 1992;**175**:1285–1290.

24. WOLLENBERG A, DE LA SALLE H, HANAU D, LIU FT, BIEBER T. Human Keratinocytes release the endogenous β -galactoside-binding soluble lectin ϵ BP which binds to Langerhans cells where it modulates their binding capacity for IgE glycoforms. *J Exp Med* 1993;**178**:777–785.
25. WOLLENBERG A, KRAFT S, HANAU D, BIEBER T. Immunomorphological and ultrastructural characterization of Langerhans cells and a novel, inflammatory dendritic epidermal cell (IDEC) population in lesional skin of atopic eczema. *J Invest Dermatol* 1996;**106**:446–453.
26. KERSCHENLOHR K, DECARD S, PRZYBILLA B, WOLLENBERG A. Atopy patch test reactions show a rapid influx of inflammatory dendritic epidermal cells (IDEC) in extrinsic and intrinsic atopic dermatitis patients. *J Allergy Clin Immunol* 2003;**111**:869–874.
27. VAN REIJSEN FC, BRUIJNZEEL-KOOMEN CAFM, KALTHOFF FS. Skin-derived aeroallergen-specific T-cell clones of Th2 phenotype in patients with atopic dermatitis. *J Allergy Clin Immunol* 1992;**90**:184–192.
28. SAGER N, FELDMANN A, SCHILLING G, KREITSCH P, NEUMANN C. House dust mite-specific T cells in the skin of subjects with atopic dermatitis: frequency and lymphokine profile in the allergen patch test. *J Allergy Clin Immunol* 1992;**89**:801–810.
29. LANGEVELD-WILDSCHUT EG, BRUIJNZEEL PLB, MUDDÉ GC, VERSLUIS C, VAN LEPEREN-VAN DIJK AG, BIHARI IC et al. Clinical and immunologic variables in skin of patients with atopic eczema and either positive or negative atopy patch test reactions. *J Allergy Clin Immunol* 2000;**105**:1008–1016.
30. SCHMID-GRENDELMEIER P, SIMON D, SIMON HU, AKDIS CA, WÜTHRICH B. Epidemiology, clinical features, and immunology of the 'intrinsic' (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis). *Allergy* 2001;**56**:841–849.
31. SEIDENARI S, MANZINI BM, DANESI P, GIANNETTI A. Positive patch tests to whole mite culture and purified mite extracts in patients with atopic dermatitis, asthma, and rhinitis. *Ann Allergy* 1992;**69**:201–206.
32. MANZINI BM, MOTOLESE A, DONINI M, SEIDENARI S. Contact allergy to dermatophagoides in atopic dermatitis patients and healthy subjects. *Contact Dermatitis* 1995;**33**:243–246.
33. INGORDO V, D'ANDRIA G, D'ANDRIA C, TORTORA A. Results of atopy patch tests with house dust mites in adults with 'intrinsic' and 'extrinsic' atopic dermatitis. *J Eur Acad Dermatol Venereol* 2002;**16**:450–454.
34. JOHANSSON C, SANDSTROM MH, BARTOSIK J, SARNHULT T, CHRISTIANSEN J, ZARGARI A et al. Atopy patch test reactions to *Malassezia* allergens differentiate subgroups of atopic dermatitis patients. *Br J Dermatol* 2003;**148**:479–488.
35. KERSCHENLOHR K, DECARD S, DARSOW U, OLLERT M, WOLLENBERG A. Clinical and immunologic reactivity to aeroallergens in 'intrinsic' atopic dermatitis patients. *J Allergy Clin Immunol* 2003;**111**:195–197.
36. JOHANSSON SGO, O'BHOURIHANE J, BOUSQUET J, BRUIJNZEEL-KOOMEN C, DREBORG S, HAAHTELA T et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;**56**:813–824.
37. KAUFMAN HS, ROTH HL. Hyposensitization with alum precipitated extracts in atopic dermatitis: a placebo-controlled study. *Ann Allergy* 1974;**32**:321–330.
38. OOSTING AJ, DE BRUIN-WELLER MS, TERREEHORST I, TEMPELS-PAVLICA Z, AALBERSE RC, DE MONCHY JG et al. Effect of mattress encasings on atopic dermatitis outcome measures in a double-blind, placebo-controlled study: the Dutch mite avoidance study. *J Allergy Clin Immunol* 2002;**110**:500–506.
39. DE BRUIN-WELLER MS, KNOL EF, BRUIJNZEEL-KOOMEN CA. Atopy patch testing – a diagnostic tool? *Allergy* 1999;**54**:784–791.