

Dose Response Study of Atopy Patch Test in Children with Atopic Eczema

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ABSTRACT

Eczematous reactions in atopic eczema (AE) patients can be elicited by epicutaneous application (patch testing) of IgE-inducing allergens (atopy patch test [APT]). The feasibility and technical aspects of this method in children were investigated in a multicenter trial in seven German university departments. Thirty children with AE (age range, 5–14 years; mean age, 9.4 years) were tested with lyophilized allergen preparations of house dust mite (*Dermatophagoides pteronyssinus*), cat dander, and grass pollen in petrolatum on uninvolved, untreated, and unabraded back skin. Allergens were applied in concentrations of 300, 1000, 3000, and 5000 protein nitrogen units per gram (PNU/g). Reactions were evaluated after 48 and 72 hours according to ICDRG guidelines and compared with the patients' allergen-specific histories of eczema flares. A total of 41% of children reacted with at least one clear-cut positive APT reaction to *D. pteronyssinus*, 17% reacted to cat dander, and 15% reacted to grass pollen. The frequency of positive reactions increased with allergen concentrations. For *D. pteronyssinus* and grass pollen, the reactivity was nearly similar, with 3000 and 5000 PNU/g, respectively, whereas with cat dander, a higher frequency of positive APT reactions was obtained with 5000 PNU/g. Positive skin prick tests (and specific IgE) were seen in 67% (40%) of patients to *D. pteronyssinus*, in 43% (43%) to cat dander, and in 57% (57%) to grass pollen. The concordance of APT results with history was 56% for *D. pteronyssinus*, 61% for cat dander, and 78% for grass pollen. No severe side effects were seen. These data may contribute to the concurrent standardization of the APT as a clinical routine diagnostic instrument in AE. In children, clear-cut positive APT reactions can be elicited with comparatively low allergen concentrations on unabraded skin. Significant clinical relevance as determined by a clear-cut patient history was highest for grass pollen as a seasonal aeroallergen. Larger dose-response studies are necessary to determine statistically based optimal

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test concentrations for different age groups. The relevance of aeroallergens for inducing flares in children with AE may be evaluated by APT. [Pediatr Asthma Allergy Immunol 1999;13(3):115–122.]

INTRODUCTION

ATOPIC ECZEMA (AE), also called atopic dermatitis or neurodermatitis, is one of the most common dermatoses in children. This inflammatory, chronic or relapsing, noncontagious, pruritic disease has a prevalence of 2 to 10% in children and young adults. Sensitization to aeroallergens and food allergens as determined by skin prick test or specific IgE antibodies is a characteristic finding in these patients.^(1,2) Among other provocation factors, aeroallergens have been demonstrated to play a role in the course of AE in a subset of patients. Exacerbation of skin lesions after contact with certain aeroallergens (mostly house dust mite/whole-body dust mites but also animal dander) and improvement after appropriate avoidance strategies were reported.^(3,4) Since the work of Mitchell et al.,⁽⁵⁾ it has been repeatedly shown that in certain patients with AE, eczematous skin lesions can be induced by epicutaneous application of aeroallergens. This test procedure, an epicutaneous patch test with allergens known to induce IgE-mediated sensitization and the evaluation of an eventually occurring eczematous skin reaction, has been called the atopy patch test (APT).⁽⁶⁾ The methods and results obtained by different groups with experimental APTs^(7–18) in the last decade have demonstrated wide variations as a result of different methodology and the lack of standardized test material (e.g., tape stripping or skin abrasion before allergen application, allergen dose, whole-body mite extracts or components thereof). As an approach to standardization, we performed APTs on nonlesional, unabraded, and untreated skin of patients with AE as well as on that of nonatopic controls.^(19–21) We have shown that using petrolatum as a vehicle and allergen doses exceeding those of skin prick test solutions improved the results of nonirritating APTs. It was also demonstrated that healthy controls and patients with respiratory atopy without a history of eczema do not react with the APT.^(19,21) A predictive pattern of distribution of eczematous skin lesions in air-exposed areas was associated with the increased probability of a positive APT reaction.^(20,21)

In a multicenter trial of a randomized, double-blind, dose-response APT, we included 30 children with AE diagnosed according to the criteria of Hanifin and Rajka⁽¹⁾ and Ring et al.⁽²²⁾ The results in adult patients enrolled in this study with other allergen dose ranges have recently been published elsewhere.⁽²³⁾ The study was designed to investigate APT dose response, safety aspects, the relationship with classic tests of IgE-mediated hypersensitivity, and clinical relevance with regard to the most frequent allergens known to elicit reactions in children with AE.

METHODS

Patients

Thirty children with AE⁽²²⁾ in actual remission (i.e., in a stable phase without acute flares of eczema)—53.3 % male patients (mean age, 9.4 ± 2.9 years; age range, 5–14 years)—were enrolled in seven university dermatology departments in Germany.

Approval by the local ethics committees and informed written consent from the patients and/or their parents were obtained. Using standardized documentation forms, the patients were examined for distribution of (residual) eczematous skin lesions. There were no children with eyelid dermatitis as the only dermatologic manifestation of atopic eczema in this study. Patient history was recorded with regard to family and personal atopic diseases, AE duration and previous exacerbations, location of eczema, and further demographic items. Prospectively, the patients were asked whether they were aware of itching and eczema flares after contact with house dust or a cat. Sudden recurring flares during the grass pollen season (May–August) as well as overall seasonal variations of eczema were also recorded. A total of 37% of patients had a history of allergic rhinoconjunctivitis, and 20% had a history of bronchial asthma. A history of urticaria was reported in 20% of patients. Eleven of the patients (37%) had a family history of AE. An overall positive family history of atopic diseases was reported in 21 patients (70%).

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APT methods and materials

Lyophilized allergens of *Dermatophagoides pteronyssinus*, cat dander, and grass pollen were introduced in concentrations of 300, 1000, 3000, and 5000 protein nitrogen units (PNU) per gram in petrolatum vehicle with 10% isopropyl myristate (allergens: Allergopharma; preparation: Hermal; both from Reinbek, Germany). After discontinuation of antihistamines and systemic or topical steroids for at least 5 days prior to investigation, the test substances were applied in a randomized double-blind design for 48 hours in large (12-mm diameter) Finn chambers (Epitest Ltd., Oy, Finland) on clinically uninvolved and non-pretreated back skin. The discontinuation of antihistamines was performed because of the additional anti-inflammatory properties of H₁ antagonists of the second generation, which are frequently prescribed in Germany and may theoretically interfere with APT reactivity. There is no experimental evidence supporting the need to discontinue these drugs before APT to date, however. APT reactions were evaluated after 48 and 72 hours. In addition, skin prick tests with the same allergens in appropriate solutions (Allergopharma) were performed. Total and specific serum IgE (CAP-RAST-FEIA; Pharmacia, Uppsala, Sweden) were determined. Positive APT reactions were graded from $\pm$ to +++, which is similar to the criteria used in classic contact allergy patch testing (German DKG standard/International Contact Dermatitis Research Group).⁽²⁴⁾ Control patch test areas were tested with vehicle-additive isopropyl myristate (10%) and a 0.5% solution of sodium lauryl sulfate as an irritant. Irritative reactions were separately evaluated and correlated to APT reactions. Prestudy standardized test reading sessions were performed by all investigators, but test application and reading were done by different persons. This means that the reactions were read by the investigator without knowledge of the (control) test sites. The APT methodology used in this study has been shown to produce no positive APT reactions with up to 10,000 PNU/g of *D. pteronyssinus*, cat dander, or grass pollen allergens in healthy controls in previous studies. In this study with children, no biopsies of positive APT sites were obtained.

Statistical analysis

Statistical analysis used SPSS software (SPSS, Chicago, IL). Fisher's exact test was used to investigate the significance of the concordance between APT results and patients' clinical history. A *p* value of 0.05 or below denoted a significant result.

RESULTS

Allergen-specific history

A total of 30% of the children included in the study reported eczema exacerbation after intense contact with house dust (e.g., cleaning, dust contact while playing), 23.3% had noticed flares after contact with a cat, and 20% were aware of AE flares after exposure to grass pollen (e.g., summer eruption, playing in a meadow).

APT dose response

The frequency of positive APT reactions increased in the investigated allergen dose range from 300 to 5000 PNU/g (Fig. 1). An example of a positive reaction (+ to +++ from 1000–5000 PNU/g) is shown in Figure 2. This figure also demonstrates a dose-dependent increase in intraindividual reaction intensity. Figure 1 shows that the percentage of clear-cut positive APT reactions for house dust mite (*D. pteronyssinus*) and grass pollen was not significantly different when 5000 or 3000 PNU/g was used; however, reactivity to cat dander was doubled by this concentration step.

Skin prick test, IgE, and APT results

A total IgE of 939 ± 1596 kU/L (range, 42–6860 kU/L) was observed in the study group of atopic children. Table 1 summarizes the percentages of clear-cut positive results for the skin prick test (wheal ≥ 3 mm), specific IgE (CAP-RAST class ≥ 1), and APT (reaction intensity $\geq +$ [i.e., erythema with infiltration]). The derived percentages of clear-cut positive reactions are compared in this table with the reaction frequencies of adult patients (*n* = 253; APT concentrations, 3000–10,000 PNU/g) in the same multicenter study.⁽²³⁾

APT dose-response [5-14y]

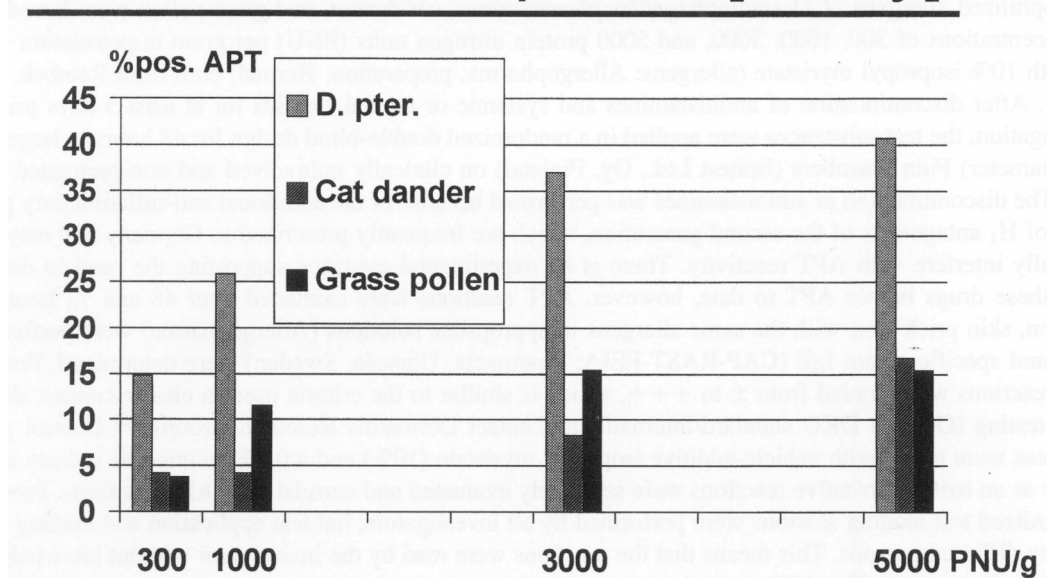


FIG. 1. Atopy patch test (APT) dose response in children (age range, 5–14 years). The percentage of positive APT results increases with the allergen dose. For house dust mite (*Dermatophagoides pteronyssinus*) and grass pollen, the maximal reactivity is nearly reached with 3000 protein nitrogen units per gram.

Clinical relevance of test results

Table 2 gives the percentages of positive/negative matching (concordance) between the APT and prospectively recorded clinical history of eczema exacerbations. For cat dander and grass pollen, a positive APT was concordant with the history as a surrogate for clinical relevance in most cases. More nonconcordant results were obtained for the house dust mite (*D. pteronyssinus*). A questionable concordance was derived when a positive reaction met with a questionable history.

Unwanted side effects

No severe side effects occurred. In 1 patient, irritation from the adhesive was noted. Itching on the arms was reported in another patient. Neither patient needed topical treatment. Control areas tested with petrolatum and isopropyl myristate remained negative in all patients. Sodium lauryl sulfate elicited questionable to irritative reactions in 12 patients, but there was no association with the APT.

DISCUSSION

The results of the study clearly show that aeroallergens are able to elicit eczematous skin lesions in children with AE when applied epicutaneously on uninvolved and untreated skin. Children are especially prone to skin contact with allergens like animal dander (pets) or grass pollen (when playing outside). In contrast to many experimental models for APT, the described methodology is suitable for routine allergy diagnosis, safe and easily tolerated by children, and can be interpreted on a clinical basis. The activity of the children from the age of 5 years on in this study did not result in additional methodologic problems compared with those in adult patients. No severe itching at the site of the APT or sleep loss was reported by the children or their parents. The individual allergen-specific history of previous eczema exacerbations was used as an indicator of relevance. We saw significant associations between positive and negative APT results with individual clinical history for cat dander and grass pollen as a seasonal allergen. The history of AE

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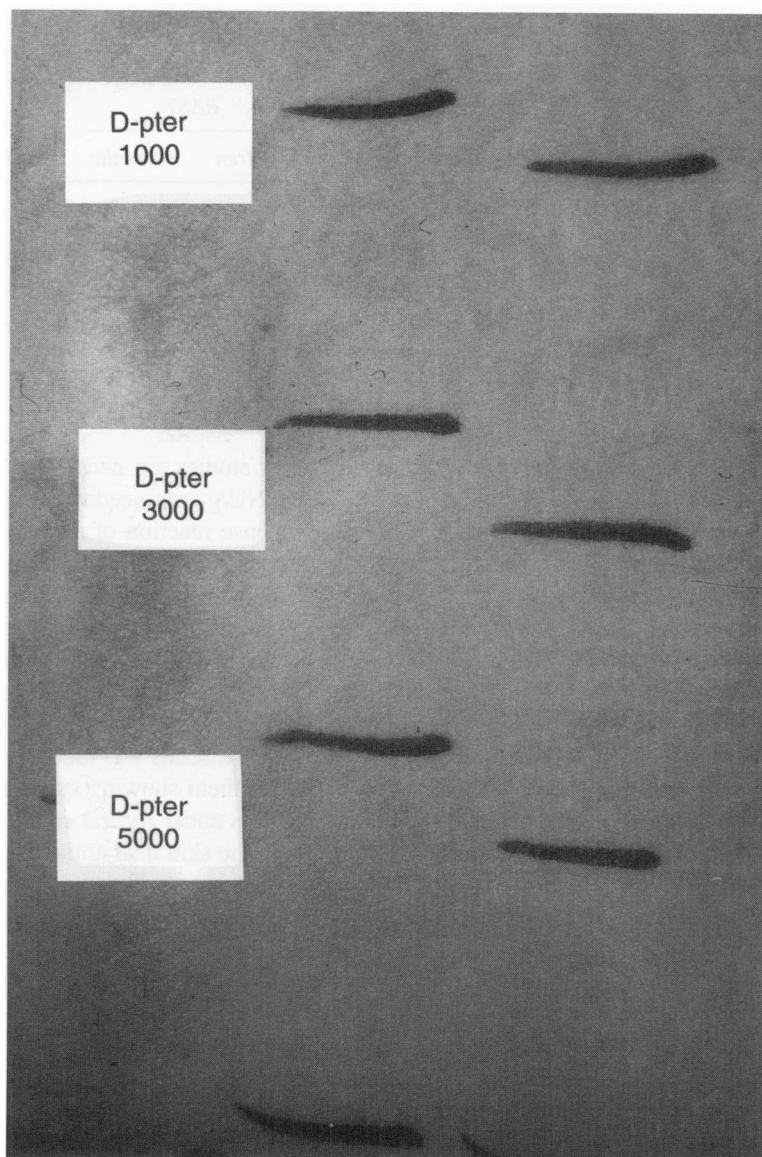


FIG. 2. Positive atopy patch test results to house dust mite (*Dermatophagoides pteronyssinus*) after 48 hours in a child with atopic eczema. Control areas remained negative. Note the dose dependency of reactions (+ to +++ from 1000–5000 protein nitrogen units per gram).

flares after exposure to house dust mite allergen is more difficult to obtain, as the patients have difficulties in recognizing dust exposure as clearly as the contact with seasonal allergens or animals. Therefore, it is not surprising that concordance between the APT and history for the allergen *D. pteronyssinus* was non-significant. In this group of 30 patients, no significant correlation between APT results and eczema pattern or a particular morphology as reported by Imayama et al.⁽¹¹⁾ was noted.

The incidence of positive patch test reactions in the patients included in this study may appear higher than the positive patch test reactivity generally expected in this age group. On the other hand, patients with AE have previously been shown to react to aeroallergens in appropriate test conditions with quite similar numbers and corresponding medical histories.^(19–23) The dose-response analysis (see Fig. 1) suggests that for *D. pteronyssinus* and grass pollen, a maximum reactivity may be reached with 3000 PNU/g in children. For cat dander, higher allergen concentrations may be required. Nevertheless, a statistically significant “op-

TABLE 1. COMPARISON OF SKIN PRICK, SPECIFIC IgE, AND ATOPY PATCH TEST RESULTS IN PATIENTS WITH ATOPIC ECZEMA

Allergen	Skin prick test		RAST		APT	
	Children	Adults	Children	Adults	Children	Adults
<i>Dermatophagoides pteronyssinus</i>	67%	59%	40%	56%	41%	34%
Cat dander	43%	54%	43%	49%	17%	12%
Grass pollen	57%	65%	57%	75%	15%	18%

Percentages in n = 30 children and n = 253 adults. Adult patient data were derived from the same study design but with allergen concentrations ranging from 3000 to 10,000 PNU/g⁽²³⁾

RAST, radioallergosorbent test; APT, atopy patch test.

timal dosage" was not established in this study. To do so, larger studies are necessary. In comparison to adult patients tested with the same methodology, where 7000 PNU/g was needed for optimal results,⁽²³⁾ children reacted at lower allergen concentrations. The dose-response reaction of a patch test may also be relevant for "irritant contact dermatitis." The APT reactivity was clearly associated with a clinical relevance (history). Also, most children with positive APT reactions had corresponding IgE-mediated sensitization. This methodologic study was not designed to investigate the mechanisms of APT-induced skin inflammation, and no biopsies were performed. Nevertheless, the role of allergen-specific IgE in the development of skin lesions after aeroallergen contact is underscored by the finding that Langerhans cells in the skin carry IgE receptors of different classes.^(25,26) Allergen-specific T cells may be activated by these Langerhans cells.^(2,27) The reason for including dust mite antigens in the patch test series was the known high frequency of specific IgE to this allergen in patients with AE, with not all of them showing symptoms of respiratory atopy. For house dust mite allergen, the penetration of the epidermis under natural conditions⁽²⁷⁾ as well as in APT sites⁽¹⁶⁾ has been demonstrated. The allergen was found in the skin near antigen-presenting Langerhans cells. Thus, these penetrating antigens may be activators of a mainly T-cell-induced atopic skin inflammation after IgE-mediated binding to Langerhans cells. This does not exclude the existence of other activating mechanisms in the complex pathophysiology of AE, however.

The APT is proposed as a tool for evaluating the clinical relevance of IgE-mediated sensitization in children. This is still not a routine test. Further studies involving allergen exposure and avoidance measures are required to show whether the identified subgroup of patients may receive special benefit from allergen avoidance strategies. APT with aeroallergens using the methodology presented here can be regarded as a type of provocation test for the epidermo-dermal compartment of the skin.

TABLE 2. ATOPY PATCH TEST: CONCORDANCE WITH HISTORY

Allergen	Concordance		
	Yes	No	Questionable
<i>Dermatophagoides pteronyssinus</i> *	56%	28%	17%
Cat dander**	61%	11%	28%
Grass pollen†	78%	6%	17%

* $p = 0.1$ (not significant).

** $p < 0.01$.

† $p < 0.001$.

Concordance was assigned when a predictive history was corroborated by a positive atopy patch test (APT) to the corresponding aeroallergen or when a negative history met with a negative APT. Questionable means a questionable history meeting with a positive APT reaction.

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