

Immunoglobulin E–Mediated Allergy Plays a Role in Atopic Eczema as Shown in the Atopy Patch Test

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Abstract: Although the pathophysiology of immunoglobulin E (IgE)–mediated allergic rhinoconjunctivitis and bronchial asthma is rather well established, the role of allergy in atopic eczema (AE) is still controversial. By a technique called atopy patch test, aeroallergens like house dust mite, animal dander, or pollen were proven as relevant trigger factors in a subgroup of patients with AE. The atopy patch test is an epicutaneous patch test with such allergens known to elicit IgE-mediated reactions, and used for the evaluation of eczematous skin reactions. In a series of single-center and multicenter studies, a method was developed, standardized, and compared with other diagnostic techniques (radioallergosorbent test, skin prick test) in AE patients. With regard to clinical history, the most specific results were obtained with the atopy patch test (allergen-dependent, 69%–92%), whereas sensitivity was higher for skin prick test (range, 69%–82%) and specific IgE (range, 65%–94%). The characterization of a patient subgroup with relevant IgE-mediated allergy may lead to more efficient avoidance and eventually even specific immunotherapy strategies in the management of AE.

Key Words: IgE, diagnostic techniques, atopy patch test, atopic eczema

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Atopic eczema (AE, atopic dermatitis, AE/dermatitis syndrome) is a clinically well-defined inflammatory, chronically relapsing, highly pruritic skin disease with a typically age-related distribution and morphology^{1–3} and a prevalence of 2% to 10% in the population.^{1,4,5} Elevated immunoglobulin E (IgE) production, especially against aeroallergens and food allergens, and/or altered unspecific reactivity are frequent findings in patients with AE and concomitant respiratory atopic diseases.^{6,7} As a multifactorial disease with a genetic background, AE has a large number of individually different trigger factors.^{8–11}

The deterioration of AE skin lesions in some patients after contact with certain IgE-inducing allergens like house dust mite, pollen, or animal dander is an old clinical observation. Consequently, allergen avoidance strategies have been used to improve the course of AE in some studies.^{12–17}

The inflammatory infiltrate of AE lesions consists to a large proportion of CD4⁺ T helper (T_H) cells. High IgE production in patients with AE is explained by an impaired balance of the T-cell populations T_H1 and T_H2, with a predominance of interleukin-4– and interleukin-13–producing T_H2 cells.^{18–23} Aeroallergens are able to penetrate the disturbed skin barrier²⁴ in patients with AE and were found in direct contact with antigen-presenting Langerhans cells.²⁵ The discovery of IgE and IgE-binding structures on the surface of epidermal Langerhans cells^{26–29} resulted in a new concept that allergy contributes to the pathophysiology of AE because all of the major components of an IgE-mediated reaction are present in the epidermis. Subsequently, the function of IgE in antigen presentation was shown by Maurer et al.³⁰ However, the question whether allergy plays a role in practice still remained: measurement of specific serum IgE and skin prick tests or intracutaneous injections of allergen solutions are clinical routine to diagnose IgE-mediated sensitizations,^{6,31} but in AE, they reveal often multiple sensitizations without clinical relevance. Furthermore, the morphology of skin test reactions (wheal and flare) does not resemble the clinical manifestation of AE, nor do they represent the appropriate dimensions of the skin immune system. An additional diagnostic tool for aeroallergen-triggered AE was needed, and the proof of concept study was done with a procedure our group called atopy patch test (APT).³²

Rostenberg and Sulzberger³³ described in 1937 a series of 12,000 patch tests with a wide variety of allergens, including aeroallergens in different patient groups. In 1982, Mitchell et al³⁴ published the first experimental patch test with aeroallergens for patients with AE. By others, eczematous reactions could be elicited with different methods, but the methodology and definition of positive reactions in these trials were not comparable.^{35–45} No clear correlation with history was obtained in larger groups of patients. Potentially irritating procedures like stratum corneum abrasion,^{34,46,47} tape stripping,^{48–50} or addition of sodium laurylsulfate⁵¹ were necessary to enhance allergen penetration. In 1989, the term atopy patch test was proposed with the following definition: an epicutaneous patch test with allergens known to elicit IgE-mediated reactions, and the evaluation of eczematous skin reactions after 48 and 72 hours.^{32,52} The first effort was to standardize APT and possibly develop a method for clinical routine giving positive results only in patients with AE and showing significant concordance to clinical relevance parameters of aeroallergen allergy.

METHODOLOGICAL STUDIES

Allergen lyophilisates of house dust mite *Dermatophagoides pteronyssinus*, cat dander, grass pollen, and in later

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studies, of birch and mugwort pollen were used. The test preparations were developed on a noncommercial basis in cooperation with several industrial allergen suppliers to maintain a high standard of batch stability and reproducibility (Hermal and Allergopharma, Reinbek, Germany; Stallergenes, Antony, France). Application in large aluminum Finn chambers (12-mm diameter) on clinically uninvolved, nonabraded, and untreated back skin was superior to the use of small Finn chambers. Reproducibility of elicited APT reactions within a mean of 16 months was 94%. Vehicles were tested in control areas in all patients and remained in general negative. At the beginning, grading of positive APT reactions was done after 48 and 72 hours according to the International Contact Dermatitis Research Group rules.^{53,54} Only reactions with infiltration were regarded as clear-cut positive (example in Fig. 1). All APT studies were performed after discontinuance of systemic antihistamines (the effect of antihistamines on APT is not known to date) and systemic and topical (test area) steroids for at least 7 days.

Role of the Vehicle

In a pilot study⁵⁵ involving 36 patients with AE, the reactions of 17 patients (47%) were graded as clear-cut positive. Control sites (petrolatum, hydrogel) remained negative, non-atopic volunteers and patients with respiratory atopy (allergic rhinoconjunctivitis) only were also negative in APT. Allergens in petrolatum vehicle elicited twice as many positive APT reactions as the same dose in a hydrogel. Thirty-six percent of patients reacted to house dust mite *D. pteronyssinus*, 22% to cat dander, and 16% to grass pollen. A *D. pteronyssinus*-positive APT was accompanied in 77% by a corresponding elevated specific IgE (skin prick test, 62%).

Dose-Response Effects and Role of Localization of Eczema

Allergen concentrations of 500, 3000, 5000, and 10,000 protein nitrogen units (PNU)/g in petrolatum were compared in another study⁵⁶ in 57 patients. The frequency of clear-cut positive APT reactions was significantly higher in patients with eczematous skin lesions in air-exposed areas (69%) as compared with patients without this predictive pattern (39%; $P = 0.02$). In the first group, the maximum APT reactivity was reached at a lower allergen dose of around 5000 PNU/g.



Allergen 200 IR/g in petrolatum

FIGURE 1. The APT with house dust mite *D. pteronyssinus* in a patient with AE. Eczematous reaction after 48 hours.

Two hundred fifty-three adult patients with AE (Table 1) participated in a randomized, double-blind, multicenter study on dose-response, safety, and clinical covariates of the APT.⁵⁷ The allergen dose with the most clear-cut results (positive or negative) in adults was found for *D. pteronyssinus*, cat dander, and grass pollen between 5000 and 7000 PNU/g. Most patients reacted only to 1 allergen, rarely to 2 or 3.

Age

In 30 children and adolescents 14 years old or younger with AE enrolled in a double-blind dose-response multicenter study,⁵⁸ a lower frequency of positive APT reactions compared with adults was seen for *D. pteronyssinus* (34% vs 41% in adults) and cat dander (12% vs 17%). For *D. pteronyssinus* and grass pollen, lower allergen doses for APT seem possible in children because maximal response rates were obtained for these allergens with 3000 PNU/g, half of the adult allergen concentration.

Allergen Standardization

Comparing different allergen standardization systems in 50 patients with parallel testing, the allergen doses of 7000 PNU/g and 200 IR/g (biological unit) were found to have similar concordance with the patients' clinical history: 71% to 73% of APT were corroborated by a corresponding positive or negative history of AE flares after contact with the specific allergen. Expressed as major allergen content, 200 IR/g correspond to 59 µg/mL *Der p1*, 9 µg/mL *Fel d1*, or 2 µg/mL *Phl p1*.

In summary, these studies showed that:

- a safe standardized APT method with positive reactions only in patients with AE was developed;
- allergen lyophilisate in petrolatum is the preferred galenic preparation;
- APT is possible on nonabraded skin without manipulation of the skin barrier function;
- allergen concentrations higher than in most prick test solutions are necessary for APT, but lower doses can be used in children;
- *D. pteronyssinus* is the most frequent allergen eliciting positive APT reactions, with reactions to pollen allergens also being very frequent; and
- high allergen-specific IgE in serum is not a prerequisite for a positive APT.

APT AND SPECIFIC IgE

The percentages of positive reactions in different test systems for IgE-mediated hypersensitivity obtained from our multicenter studies are given in Table 1. These and previous APT studies showed that positive APT occurred less frequently than positive skin prick tests or radioallergosorbent tests (RASTs) to the same allergen. Logistic regression analysis⁵⁷ revealed patient's history, skin prick test, and specific corresponding IgE for *D. pteronyssinus*, cat dander, and grass pollen as most important significant predictors of a positive APT ($P < 0.001$). However, the cross-tabulation also confirmed that high allergen-specific IgE in serum is not mandatory for a positive APT (example in Table 2), the same holds true for the correlation with skin prick tests. A European

TABLE 1. Clinical Covariates of the APT in 2 Multicenter Studies With Different Allergen Standardization

	Skin Prick		sIgE		APT		History	
	A	B	A	B	A	B	A	B
<i>D. pteronyssinus</i>	59	56	56	56	34	39	52	34
Cat dander	54	44	49	46	12	10	23	30
Grass pollen	65	57	75	59	18	15	33	31
Birch pollen	65	49	65	53	11	17	13	20

A indicates German multicenter⁵⁷ (7 centers, N = 253 adults, 3000–10,000 PNU/g); B, European multicenter⁵⁹ (6 countries, 12 centers, N = 314, 200 IR/g). Values are expressed as percentages.

multicenter study⁵⁹ on standardized APT in 6 countries (n = 314) showed a subgroup of 7% APT-positive AE patients without any positive skin prick test or elevated specific IgE in the investigated allergen panel (Fig. 2). Nevertheless, these reactions can be of clinical relevance and immunological specificity.⁶⁰ In conclusion,

- the APT may give further diagnostic information in addition to patient’s history and classical tests of IgE-mediated hypersensitivity;
- the role for IgE in the reaction mechanism of APT is corroborated because in most APT-positive patients, elevated specific IgE was found compared with those with negative APT; and
- a cellular mechanism without direct involvement of IgE may be hypothesized to explain the clear-cut positive APT reactions in a subgroup of AE patients.

IgE-MEDIATED SENSITIZATION AND APT: DIAGNOSTIC PRECISION

Unlike in food allergic patients, a “golden standard” of provocation of aeroallergen-induced AE is not established. The prospectively obtained history of allergen-induced exacerbations of AE, especially in a seasonal allergen, can be used to evaluate the clinical relevance of an APT result like in conventional patch testing. Rajka³ reported on the phenomenon of “summer eruption,” that is, eczema flares during spring and summer, the pollen seasons of birch and grass, in one third of patients with AE. According to our results, one third of patients with specific IgE to grass pollen can have a positive APT reaction to this allergen.⁵⁷ In a study on the influence of grass pollen on AE,⁶¹ we tested 79 patients with an APT with 10,000 PNU/g grass pollen allergen mixture in petrolatum and simultaneously with 10 mg of dry unprocessed grass pollen of *Dactylis glomerata*. Significantly higher frequencies of positive APT occurred in patients with a history of exacerbation of AE in the summer months of the previous year or in direct contact with grass (n = 12, 75% had

positive APT) compared with patients without this history (n = 67, 16% had positive APT; *P* < 0.001). Sensitivity and specificity of APT and classical tests for IgE-mediated sensitization are given in Table 3. The standardized APT also correlated with a predictive eczema pattern, skin prick test, and specific IgE to grass pollen (*P* < 0.01). Moreover, unprocessed grass pollen also elicited eczematous skin reactions on nonpretreated skin of patients with AE, significantly associated to history and a positive standardized APT with lyophilisate. Again, in healthy and rhinoconjunctivitis controls, no positive reactions were observed.

In a larger patient group in the German multicenter study,⁵⁷ APT results of *D. pteronyssinus*, cat dander, and grass pollen were also statistically significantly associated with clinical history (*P* < 0.001, χ^2 and logistic regression; birch pollen, *P* = 0.1). Thus, sensitivity and specificity of different diagnostic tests could be compared. Allergen-dependent, the APT showed a higher specificity with regard to clinical relevance of an allergen than skin prick test and specific IgE, but also in most allergens, a lower sensitivity (Table 3). In a subgroup of these patients, specific activation and proliferation of T cells in peripheral blood was compared with the patient’s APT result.⁶² Positive APT reactions were significantly more frequent in patients with elevated CD54⁺ or CD30⁺ T cells after in vitro stimulation with the corresponding allergen. In addition, positive APT results were associated with an allergen-specific lymphocyte proliferation (*P* < 0.001). Positive APT reactions were not associated with disease severity in the SCORAD (scoring atopic dermatitis) system.^{62,63}

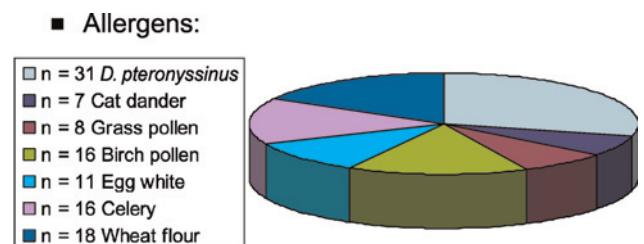


FIGURE 2. In 53 (17%) of 314 patients of a European multicenter study,⁵⁹ positive APT reactions, but negative corresponding skin prick test/specific IgE results, were observed (1 allergen, n = 26; 2 allergens, n = 12). In 22 of these patients with a clear-cut positive APT result, no positive skin prick test or elevated specific serum IgE of the investigated allergen panel was seen (7% of total). The figure shows that all allergens contribute to these reactions.

TABLE 2. Cross-Tabulation of APT and Specific IgE to House Dust Mite *D. pteronyssinus*, Results of a Multicenter Study⁵⁷

APT 48-h Results in Adult Patients for House Dust Mite <i>D. pteronyssinus</i>	sIgE		Total
	Negative	Positive	
APT negative	49	29	78
APT positive	13	60	73
Total	62	89	151

From APT biopsies, allergen-specific T cells have been cloned. In serial biopsies, T cells showed a characteristic TH2 secretion pattern (interleukin-4, -13) at 24 hours, whereas after 48 hours, a TH1 pattern (interferon-γ) like in chronic AE lesions was predominant.⁶⁴⁻⁶⁶ Taken together, these findings:

- argue against the interpretation of APT results as irritative or nonspecific;
- suggest that pollen are involved in AE flares in some patients previously diagnosed as having UV-triggered eczema;
- demonstrate the clinical relevance of positive APT reactions and the different compartments of allergic inflammation that can be investigated with skin prick test, specific serum IgE determination, and APT;
- show that allergen-specific T cells and IgE play a role in the pathophysiology of APT reactions; and
- sustain the concept that AE is not only a disease of dry skin or barrier dysfunction, but also an allergic disease.

THE FUTURE OF THE APT

Appropriate allergen-specific avoidance strategies^{13,14,16,67,68} are recommended in patients showing positive APT reactions. The identified subgroup of patients may profit extraordinarily from allergen avoidance, but controlled studies using specific provocation and elimination procedures in patients with positive and negative APT results are still necessary. Standardization of major allergen content and achieving an increase in the sensitivity of APT are important goals of ongoing trials. The combination of APT and specific IgE results may lead to higher diagnostic precision, but the problem of discordant tests has to be solved. Meetings of most European groups performing APT for clinical use in 1997, 1998, and 2003 resulted in a consensus APT reading key of the European Task Force on Atopic Dermatitis (Fig. 3).^{60,69} The European multicenter trial also started the investigation of food allergen patch testing with lyophilisates in petrolatum. The development of a standardized APT for food allergy is a future plan, as well as a study on the mechanisms of APT reactions involving both patients with intrinsic and extrinsic

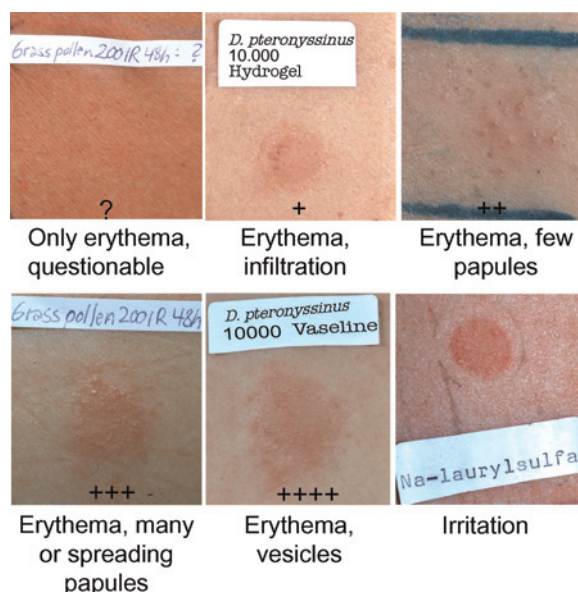


FIGURE 3. The APT reaction grading key (2003 European Task Force on Atopic Dermatitis consensus).

AE and investigating the role of the Fcε receptor I and allergen-specific T-cell populations. Furthermore, the APT will be used in trials on topical and systemic therapy for AE and is evaluated as itch model.^{70,71} Other aeroallergens of regional significance are to be standardized. A test for the clinical relevance of an aeroallergen sensitization that can be applied in the allergist's practice may evolve soon. The APT may also be valuable in selecting patients for specific immunotherapy. To solve the remaining tasks in due time and to overcome the methodological inconsistencies of different groups, the organization of international multicenter studies is necessary. A recent European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network position paper focused on clinical results and unresolved problems of APT.⁷²

CONCLUDING REMARKS

The described APT methodology was evaluated in several hundreds of patients with AE. In a large subgroup of them, IgE-dependent allergic reactions that are elicited by the transdermal route play a pathophysiological role. For patients with aeroallergen-triggered disease, the APT may provide an important diagnostic tool, a provocation test of the skin in analogy to the specific provocation methods in respiratory atopy. As in respiratory atopy, the results of our studies sustain B. Wüthrich's concept of extrinsic/allergic versus intrinsic/idiopathic AE.⁷³

Positive APT results were obtained in some AE patients with negative skin prick tests and RAST, but predictive history. According to the previously mentioned concept, these cases may also be classified as "extrinsic," and with the background of the recently proposed novel nomenclature for allergy,⁷⁴ we suggested to diagnose these cases as "non-IgE-associated AE (dermatitis syndrome)."⁶⁰

TABLE 3. Sensitivity and Specificity of Different Diagnostic Methods in 2 Studies With Patients With AE

Test	Sensitivity*	Specificity*
Single-center study, n = 79 (allergen, grass pollen)		
Skin prick	100	33
RAST	92	33
APT	75	84
APT multicenter study, n = 253 (3 allergens)		
Skin prick	69-82	44-53
RAST	65-94	42-64
APT	42-56	69-92

Better results are obtained with a seasonal allergen. Data from Ref. ⁶¹ and Ref. ⁵⁷
 *Referring to predictive history of eczema exacerbations in pollen season or in direct contact with allergen, excluding questionable cases, depending on allergen.
 Values are expressed as percentages.

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