The Clinical Relevance of Various Hypersensitivity Tests in Patients with Atopic Dermatitis as Assessed by Their History, SCORAD Changes, and Number of Days with Need of Anti-Inflammatory Treatment

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Immediate and delayed hypersensitivity reactions can play a role in the pathogenesis of atopic dermatitis (AD). We tested 71 patients (median age 5 years) with AD for hypersensitivity to grass and birch pollen, *Dermatophagoides pteronyssinus*, and *Dermatophagoides farinae* using atopy patch test (APT), skin prick test (SPT), and specific IgE measurement. The sensitivity (SE) and specificity (SP) of the tests were calculated on the basis of personal history of AD exacerbation, clinical AD score (SCORAD) changes, and the number of days with need for topical anti-inflammatory treatment (AITD) in relation to exposure to the allergens being tested. APT was positive in 45 patients, mostly to *D. farinae* ($n=37$). SPT and/or specific IgE were positive in 42 subjects, in most cases to grass and birch pollen ($n=29$). SE of APT reached 33%–56% for history, 33% for SCORAD, and 0%–60% for AITD; SP of APT was comparable for all three assessment standards (history, SCORAD, and AITD) (48%–67%). SE of SPT/specific IgE was higher for history (26%–63%) than for the other two standards of assessment (0%–67%); SP of SPT/specific IgE was also highest for history (69%–91%), and lower for SCORAD (59%–87%) and AITD (65%–80%). AD is often associated with hypersensitivity; its influence on AD, however, is clinically significant only in a minor group of patients. While personal history and SCORAD changes present themselves as possible standards in the evaluation of clinically relevant hypersensitivity in AD patients, the anti-inflammatory treatment days (AITD) appears to be unsuitable for this purpose.

Introduction

HYPERSENSITIVITY TO ALLERGENS belongs among various factors that participate in the pathogenesis of atopic dermatitis (AD). Even though the exact role of hypersensitivity in AD is not yet fully understood, it is known that contact with an allergen can lead to a worsening of the condition, and, conversely, that implementation of an allergen avoidance regimen can lead to its improvement. While food allergens have long been considered to play a major role in AD, there is also increasing evidence that aeroallergens are involved.^{1,2} Two different types of hypersensitivity reactions can play a role in AD pathogenesis: the first being immediate, allergen-specific, and IgE-mediated, and the second delayed, allergen-specific, and T cell-mediated.

Immediate-type hypersensitivity is usually diagnosed by skin prick tests (SPTs) or by measurement of serum-specific IgE. The disadvantage of SPT is the need for the discontinuation of topical steroid and antihistamine treatment, which can lead to a worsening of the preexisting AD. In addition, the requirement of intact skin cannot always be fulfilled; this

is especially true in childhood, when AD lesions are commonly localized on the volar side of the forearms where SPT is usually performed. In contrast, specific IgE measurement—though more expensive—has no such limitations.

Delayed, allergen-specific T-cell reactions also play an important role in the pathogenesis of AD, but since it is not possible to detect these reactions using tests of immediate-type hypersensitivity, a different kind of test needs to be used in their diagnosis. The patch test is a standard method used for testing of delayed-type hypersensitivity reactions to contact allergens. The atopy patch test (APT)^{1–4} poses its modification, which is performed with allergens also known to elicit immediate-type hypersensitivity reactions. In the diagnosis of food allergy, APT can increase the diagnostic benefit of SPT and/or specific IgE measurement, even if it is often necessary to verify results by a double-blind, placebo-controlled food challenge. Sensitivity and specificity of APT varies depending on the type of food allergen.^{2,5}

A relationship between exposure to certain aeroallergens and worsening of AD has also been repeatedly observed,^{6,7} and an impaired epidermal barrier in AD is believed to make

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allergen penetration through the skin easier. As concerns the assessment of the possible role of aeroallergens as triggering factors of AD, APT has shown higher specificity with regard to clinical history compared with both SPT and specific IgE measurement.^{1,2,8} Comparison of T cells obtained from naturally occurring skin lesions with those from patch test-induced lesions has shown equal specificity to aeroallergens.⁹

Since the diagnostics of hypersensitivity in AD raised our interest in its possible contribution to the better understanding of AD pathogenesis and in finding new management approaches, we decided to investigate the frequency of hypersensitivity to common aeroallergens in patients suffering from AD and to evaluate the clinical relevance of hypersensitivity as detected by APT, SPT, and specific IgE measurement.

Our clinical study of patients with AD was carried out from 2006 to 2013. The aims of the study were the following:

- (1) To discover the frequency of immediate- and delayed-type hypersensitivity to common aeroallergens using APT, SPT, and specific IgE measurement;
- (2) To calculate the specificity and sensitivity of the above tests on the basis of changes resulting from patients' exposure to the tested allergens in (a) personal history of AD symptom worsening, (b) clinical AD score (SCORAD), and (c) need for topical anti-inflammatory treatment.

Materials and Methods

Our study group included 71 patients (37 males and 34 females) with AD; 10 patients also suffered from allergic rhinitis, 3 subjects had bronchial asthma, and 9 subjects had both allergic rhinitis and bronchial asthma. Patients were enrolled based on Hanifin and Rajka diagnostic criteria,¹⁰ and ranged in age from 1 to 34 years (with a median age of 5). AD severity was evaluated using the SCORAD clinical scoring system; the mean score was 17.9 ± 9.5 . The study was approved by the Ethics Committee of the University Hospital in Pilsen, and written informed consent was obtained from adult subjects or children's parents.

Enrolled patients were tested using APT, SPT, and specific IgE measurement for hypersensitivity to four common aeroallergens (grass pollen mixture, birch pollen, *Dermatophagoides pteronyssinus*, and *Dermatophagoides farinae*). Patients or their parents completed a questionnaire on their personal history of AD exacerbations resulting from exposure to these allergens. In a subgroup of patients, the influence of exposure to the tested allergens was also assessed in terms of patients' AD score (SCORAD) and need for topical anti-inflammatory treatment. The subgroup included 30 patients (16 males and 14 females, median age of 4.5 years) with AD.

Patients were then randomized into either the active or control treatment group. Patients in the active group were equipped with allergen-impermeable covers for mattresses, pillows, and quilts (Protec'Som) and with information on the management of a house dust mite avoidance regimen; patients assigned to the control group initially applied no mite avoidance regimen. All subjects were then assessed monthly using SCORAD for a study period of 1 year during which they also recorded days with need of anti-inflammatory treatment (AITD).

To avoid the confounding factor of possible pollen allergy, the house dust mite avoidance regimen was applied for 6 weeks strictly out of pollen season (September–March). During these 6 weeks, SCORAD was assessed at three different times: initially and then after 3 and 6 weeks. After 6 weeks of mite avoidance the treatment groups were crossed: mite avoidance measures were applied to subjects from the control group and, inversely, the same measures were discontinued in subjects from the formerly active group. The effectiveness of the mite avoidance regimen was monitored by measuring mite allergen concentrations (Der p 1, Der f 1) in dust sampled from subjects' beds at three separate times: initially, after 6 weeks of avoidance application, and finally after 6 weeks of avoidance discontinuation. The procedure of obtaining the allergen samples was performed in accordance with van Strien's study¹¹; the ELISA allergen concentration evaluation was done according to the recommendations of the manufacturer (Indoor Biotechnologies).

Finally, statistical evaluation was done.

Atopy patch test

Allergenic extracts in petrolatum (concentration 200 IR/g; Stallergènes) were applied in FinnChambers® (Ø 8 mm; Epitest Ltd., Oy) onto clinically uninvolved and cleaned skin of the upper back. Pure petrolatum was used as a negative control. Reading was performed 48 and 72 h after the application of allergens; occlusion time was 48 h. The test was evaluated according to the revised 2003 European Task Force on Atopic Dermatitis (ETFAD) key. Reaction $\geq +$ was considered positive.

Skin prick test

Allergenic extracts (concentration 100 IR/mL; Stallergènes) were applied onto the skin of the volar side of the forearm using a standard procedure. Mean wheal diameter ≥ 3 mm was considered positive.

Serum-specific IgE levels measurement

Serum-specific IgE levels were measured using the chemiluminescent enzyme immunoassay technique (Immulite®; DPC/Siemens). Specific IgE level ≥ 0.7 IU/mL was considered positive.

Personal history

All subject or their parents completed a standardized YES/NO questionnaire on AD worsening as a consequence of exposure to the allergens being tested, that is, during grass pollen or birch pollen season, or after contact with house dust.

SCORAD changes

The AD clinical score (SCORAD) was evaluated monthly throughout the whole study period of 12 months. Pollen season was defined on the basis of pollen concentration reports. The median of SCORAD for each of the three observed periods was calculated (birch or grass pollen season, the duration of the application/discontinuation of the mite avoidance regimen, the period out of pollen season) and its change was evaluated as a comparison of time of exposure/nonexposure. A SCORAD change of ≥ 10 points was considered positive.¹²

Anti-inflammatory treatment days

Patients recorded their use of topical anti-inflammatory drugs (corticosteroids and calcineurin inhibitors) for the whole study period. Anti-inflammatory treatment days (AITD) was expressed as the percentage of days with need for topical treatment during the observed periods (birch or grass pollen season, mites avoidance/its discontinuation, the period out of pollen season). The change of AITD was evaluated as a comparison of the periods of exposure/nonexposure. A change $\geq 10\%$ in AITD was considered as positive.

Results

APT and specific IgE were performed in all subjects; SPT was performed in all but one patient because of skin lesions on his forearms. No patient experienced any significant adverse reaction related to the performed tests.

At least one positive APT reaction was seen in 45 patients (63%), most frequently to house dust mites (38 patients), followed by birch pollen (21 patients) and grass pollen (18 patients) (see Fig. 1). In 26 patients, APT was positive for more than one unrelated allergen. Five patients showed positive APT reactions to all allergens being tested, and 17 patients (24%) had a positive result for APT but were nonetheless negative for both other measures (SPT and specific IgE).

At least one of the tests of immediate-type hypersensitivity detection (SPT and specific IgE) was positive in 42 patients (59%); the most frequent allergens causing immediate hypersensitivity reactions were birch and grass pollen (29 patients each), followed by house dust mites (18 patients) (see Fig. 2). Polyvalent sensitization of the immediate type was seen in 28 patients, and only immediate (but not delayed) hypersensitivity was proven in 14 patients (20%). Both types of hypersensitivity were simultaneously present in 28 patients (39%) (see Fig. 3). No hypersensitivity was found in 12 patients (17%).

The specificity and sensitivity values of particular tests are listed in Table 1. On the basis of personal history, APT showed a sensitivity of between 33%–56%, and a specificity of 43%–87%. The sensitivity of immediate-type hypersensitivity tests (SPT and specific IgE) varied between 26%–63%, and their specificity reached 69%–91%.

Assessment on the basis of SCORAD changes in relation to allergen exposure showed an APT sensitivity of 33%, and

FIG. 1. Positive atopy patch test (APT) results.

FIG. 2. Positive skin prick test (SPT) and specific IgE results.

specificity of 52%–67%. The sensitivity of SPT and specific IgE varied between 0%–67% and their specificity between 59%–87%.

Assessment on the basis of changes in topical anti-inflammatory treatment use (AITD) showed low APT sensitivity for all tests (0%–60%), and APT specificity was lower (48%–62%) than that of SPT and specific IgE (65%–80%).

Measurement of Der p 1 and Der f 1 concentrations in patient's beds revealed a significant decrease after introduction of the mite-avoidance regimen for all but five patients where allergen concentrations were low in all three measurements.

Discussion

The importance of hypersensitivity detection in patients with AD is indisputable: at least one of the tests was positive in 83% of our patients. While this percentage is rather high, it is similar to other studies.^{1,8,13} The coincidence of both types of hypersensitivity was also frequent (58%) and may be related to the role of specific IgE antibodies in the pathogenesis of APT reactions. Allergen-specific IgE can bind to Langerhans cells in epidermis, enhancing antigen presentation to T lymphocytes.¹⁴ Initially, T cells display a Th2 secretion pattern, but later switch to a Th1 pattern.¹⁵ The observed frequencies of immediate and delayed-type

FIG. 3. Positive APT with or without simultaneous SPT and/or specific IgE positivity.

TABLE 1. THE SPECIFICITY AND SENSITIVITY OF THE TESTS PERFORMED

	APT			SPT			Specific IgE		
	History SE/SP (%)	SCORAD SE/SP (%)	AITD SE/SP (%)	History SE/SP (%)	SCORAD SE/SP (%)	AITD SE/SP (%)	History SE/SP (%)	SCORAD SE/SP (%)	AITD SE/SP (%)
Birch	33/73	33/59	40/60	44/78	0/70	40/76	58/69	0/59	60/68
Grass	56/87	33/67	0/62	53/75	67/74	25/69	63/71	33/67	25/65
<i>Der. pter.</i>	39/51	33/52	0/48	29/81	33/78	0/72	26/87	33/87	0/80
<i>Der. far.</i>	39/43	33/52	0/48	29/91	33/87	0/80	26/87	33/87	0/80

APT, atopy patch test; SPT, skin prick test; AITD, anti-inflammatory treatment day; SE, sensitivity; SP, specificity; *Der. pter.*, *Dermatophagoides pteronyssinus*; *Der. far.*, *Dermatophagoides farinae*.

hypersensitivity in our patients were very close to each other (59% and 63% respectively), which differs from previous results^{1,2} where frequency of immediate-type hypersensitivity was higher, maybe due to different age stratification of our study group. The polyvalent sensitization, prevailing in both types of hypersensitivity, is noteworthy, and may reflect the general tendency of the immune system to generate inappropriate reactions targeted at various nonrelated allergens. Nevertheless, it is apparent that APT enables us to identify a subgroup of patients who, despite displaying negative results when tested by commonly used hypersensitivity tests, nonetheless have hypersensitivity that can substantially influence their AD.

Previous studies^{1,2,8} have found the specificity of APT to be higher as compared to immediate-type hypersensitivity tests (SPT and specific IgE), and our results were in some ways similar and in some ways different: while our APT sensitivity and specificity were in line with previous findings, immediate type hypersensitivity tests showed lower sensitivity and higher specificity for both SPT and specific IgE than these previous studies did. One possible explanation could be the different age composition of our study group: our median patient age of 5 years was lower than the 22 and 25.5 years respectively of the comparison studies.^{2,8} It also may be of importance that an immediate hypersensitivity reaction to aeroallergens is less frequent in young children.¹⁶ Concomitant respiratory allergy might also have some confounding effects since the detected hypersensitivity could rather be related to respiratory allergy. Additionally, the difference in results can simply reflect our smaller study group size and each deviation could thus have had stronger impact on the final results.

When evaluating the sensitivity and specificity of hypersensitivity tests, the effectiveness of the use of SCORAD and AITD as new gold standards proved similar (SCORAD) or lower (AITD) than the use of personal history. In general,

assessment on the basis of SCORAD changes provided slightly lower specificity of results than did personal history, and sensitivity was comparatively even lower, especially for SPT/specific IgE and pollen allergens. We could speculate that this was due to SCORAD's "true" correction of inaccurate information obtained through the personal history. The use of AITD changes as a standard for hypersensitivity test assessment showed poor and inconsistent results. A possible explanation could be strong subjective influence on the use of topical anti-inflammatory drugs, for example, corticophobia in patients/parents.

It might be important that the clinical relevance of the results increased substantially in cases of coincidence of immediate and delayed-type hypersensitivity to the same allergen (see Table 2). In our opinion, this finding may correspond to the parallel development of immediate and delayed hypersensitivity.^{14,15}

In patients with AD, the prevalence of a hypersensitivity diagnosis is high. Its clinical importance, however, appears to be limited, and only a relatively small portion of AD patients is clinically influenced by exposure to aeroallergens. The simultaneous presence of both immediate and delayed hypersensitivity to the same allergen has higher clinical relevance than either of these types of hypersensitivity alone. Change in SCORAD presents itself as a possible means of evaluating the clinical relevance of hypersensitivity to aeroallergens; recording changes in the anti-inflammatory treatment days (AITD), however, do not appear to be suitable in the assessment of clinical relevance of hypersensitivity in AD.

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Author Disclosure Statement

Authors declare no conflict of interest.

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TABLE 2. THE SPECIFICITY AND SENSITIVITY OF RESULTS IN CASES OF SIMULTANEOUS POSITIVITY TO THE SAME ALLERGEN

	History		SCORAD		AITD	
	SE (%)	SP (%)	SE (%)	SP (%)	SE (%)	SP (%)
Birch	31	86	0	81	20	84
Grass	50	96	33	89	0	85
<i>Der. pter.</i>	28	89	50	88	0	81
<i>Der. far.</i>	33	88	67	88	0	81

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