

Zbigniew SAMOCHOCKI
Witold OWCZAREK
Stanisław ZABIELSKI

Department of Dermatology,
Central Clinical Hospital of Military
Institute of Medicine,
ul. Szaserów 128,
00-909 Warsaw, Poland

Reprints: Z. Samochocki
Fax: (+48) 228105520
<owczarekmw@poczta.onet.pl>

Can atopy patch tests with aeroallergens be an additional diagnostic criterion for atopic dermatitis?

The complex pathomechanisms underlying skin lesions in atopic dermatitis (AD) result in variations of the clinical picture and frequent diagnostic difficulties. The purpose of this study was to evaluate the usefulness of atopy patch tests (APT) for aeroallergens in the diagnosis of AD. The study involved 115 adult patients with AD and 98 healthy volunteers (the control group). APTs for cat dander allergens, birch pollen, a mixture of house dust mite species and a mixture of 5 grass pollen allergens were applied for both groups. Positive reaction to at least one test allergen was found in 53.9% patients compared to 6.2% in the control group ($p < 0.001$). The most frequent hypersensitivity (45.2%) observed was to house dust mite allergens. Polyvalent allergy to 2–4 allergens was found in 56.5% patients. The specificity of tests exceeded 75%, whereas the sensitivity varied from 18 to 66%. Conclusions: 1. Atopy patch tests, which are characterised by considerable specificity, confirm the role of polyvalent contact hypersensitivity to aeroallergens in the development of atopic dermatitis. 2. Positive aeroallergen ATP results are observed in the majority of patients and can thus be regarded as an additional diagnostic criterion in atopic dermatitis.

Key words: aeroallergens, atopic dermatitis, atopy patch test

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In 1977 Hanifin and Lobitz [1] published their diagnostic criteria for atopic dermatitis (AD), which were subsequently modified by Hanifin and Rajka in 1980 [2]. These criteria still serve as the basic tool in the diagnosis of AD. Among so-called minor criteria in this classification are positive skin-prick test (SPT) results for food and/or air-borne allergens (aeroallergens), which are seen in 66–88% of patients [2, 3]. In adults these tests mainly detect hypersensitivity to aeroallergens [3]. Laboratory studies have also revealed elevated specific anti-aeroallergen IgE (sIgE) levels in 73% of adult patients with AD [4]. Together with clinically evident flare-ups of AD following aeroallergen challenge, these findings have confirmed a significant role of type I hypersensitivity response in the aetiopathogenesis of AD. However, this mechanism cannot account for all findings associated with aeroallergen intolerance [5–7]. It has also been demonstrated that hypersensitivity to aeroallergens in patients may be associated with a type IV response or be of mixed (I/IV) origin [8]. Patch tests are an accepted method of detecting contact hypersensitivity, where tested combinations of non-protein origin (haptens) cause a topical eczema reaction via IV allergic mechanisms associated with Langerhans cells and Th1 lymphocytes [9]. However, atopic patch tests are epidermal contact tests made with protein allergens evoking standard IgE-dependent reactions [10]. The topical reaction, defined with IgE-dependent contact eczema, does not differ clinically from conventional contact eczema. It is caused via presenting protein allergens to Th2 lymphocytes

by Langerhans cells covered with specific IgE [11]. These findings seemed to provide a rationale for performing patch tests for aeroallergens in order to detect factors that provoke or exacerbate AD through a contact hypersensitivity mechanism [12].

The aim of our study was to assess the utility of atopy patch tests for aeroallergens in the diagnostic work-up for atopic dermatitis.

Material and methods

Patients and control subjects

The study comprised 115 AD patients (63 females and 52 males), aged 18 to 45 years (mean 25.5). The diagnosis was made when at least three major and three minor features of Hanifin and Rajka criteria were met [2]. Forty seven out of 115 (40.9%) AD patients examined also showed allergic rhinitis, 35/115 (30.4%) showed allergic conjunctivitis, and 19/115 (16.5%) atopic asthma. Patients were diagnosed and treated in the Department of Dermatology, Central Clinical Hospital of Military Institute of Medicine in Warsaw during the years 2002–2004. The study was conducted during the period of complete remission of skin changes. The patients were not on drugs of a type, or during an administration time, which could exert any impact on the results of the examinations performed.

A control group was composed of 98 gender- and age-matched healthy volunteers with negative family and individual history of atopy.

The patients examined were informed about the aim of the study and gave informed assent. The agreement of the Local Ethics Committee was also obtained.

Allergens

Allergenic material consisted of extracts of individual allergens or allergen mixtures: 1. a mixture of the house dust mite species *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, 2. common birch (*Betula alba*) pollen, 3. A mixture of five species of grass: orchard grass *Dactylis glomerata*, smooth-meadow grass *Poa pratensis*, perennial ryegrass *Lolium perenne*, sweet vernal grass *Anthoxanthum odoratum* and timothy *Phleum pratense*, 4. cat dander.

Atopy patch test

Atopy patch tests (APT) were performed on clinically uninvolved skin of the back using commercially available reagents of Stallergenes Company (France). Squares of blotting paper of 1 × 1 cm, soaked in the solutions of the allergens being examined, as well as the control test which was composed of the vehicle (ointment base) *i.e.* white Vaseline, were applied on the skin. Subsequently, the blotting paper was covered with plastic foil (1.5 × 1.5 cm) for occlusion. Then hypoallergic adhesive tape was applied to fix the test dressings. Reagents composed of allergens in a concentration of 200 IR were used in the study [13, 14]. The patches were removed after 48 hours and the findings were assessed at 72 hours after the test application. Tests were classified as positive if the reaction on the skin was estimated at least as one plus (+). The following scale was employed: (–) lack of any signs, (+/–) doubtful reaction, (+) erythema, infiltration, (++) erythema, a few papules (up to 3), (+++) erythema, papules (4 and more), (+++++) erythema, numerous, disseminated papules, (+++++) erythema, vesicles, exudates [13].

Statistical analyses

The statistical analyses involved the chi-squared test with Yates's correction for small groups, at a confidence level of $p < 0.05$.

In order to compare the strength of variable results, the sensitivity (SE) and specificity (SP) of APT was calculated, formulating the result in percentage according to the following formula:

$$SE = \frac{WD}{WD + FN} \quad (1)$$

$$SP = \frac{WN}{WN + FD} \quad (2)$$

where WD defines the positive history of exacerbations of skin lesions following exposure to the aeroallergen and a positive APT to this allergen, FN – positive history of exacerbations, negative APT, WN – negative history of exacerbations, negative APT, FD – negative history of exacerbations, positive APT [15]. In the case of plant pollen allergens, the exacerbation of skin changes reported in history, referred to the period of exposure to pollen, which

in Poland is the second half of April and the first week of May for birch pollen, and June and the first half of July for grass pollens.

Results

Sixty three patients, out of 115 (54.8%) reported the development of pruritus and/or exacerbation of the eczematous lesions following exposure to dust. The respective percentages associated with intolerance of birch pollen, grass pollen and cat dander were 46.1 (53/115), 46.1 (53/115) and 33.0 (38/115).

Hypersensitivity to the mixture of house dust mites was seen in 52/115 (45.2%) patients, to birch pollen in 37/115 (32.2%) patients, to the mixture of grass pollen in 26/115 (22.6%), and to cat dander in 18/115 (15.7%) patients (figure 1). In the control group, 6/98 (6.2%) patients were hypersensitive to the mixture of house dust mites on patch testing.

A total of 62 (53.9%) of the 115 patients in the study group were found to be hypersensitive to at least one of the study aeroallergens or their mixtures on patch testing. In the control group, the corresponding percentage of ATP-positive patients was 6.2% (6/98) and the difference between these values was statistically significant at $p < 0.001$. Hypersensitivity to one group of study allergens was seen in 27/62 (43.5%) of APT-positive patients, while 13/62 (21.0%) patients were hypersensitive to two groups of aeroallergens, 8/62 (12.9%) were hypersensitive to three groups of aeroallergens and 14/62 (22.6%) were hypersensitive to all four groups of aeroallergens (figure 2).

The correlation between positive APT and positive history of exacerbation in the case of exposure was from 18.5% for cat dander to 66.6% for the mixture of house dust mites. The specificity of the atopy patch test ranged from 75.9% for birch pollen to 85.7% for cat dander (table 1).

Discussion

Skin lesions associated with AD are non-specific since they also occur in the course of other dermatoses. There are no diagnostic criteria based on histopathological findings and the laboratory findings may vary from patient to patient. Even though the criteria developed by Hanifin and Rajka [2] embrace a variety of the features of this condition, AD may be difficult to diagnose in atypical cases.

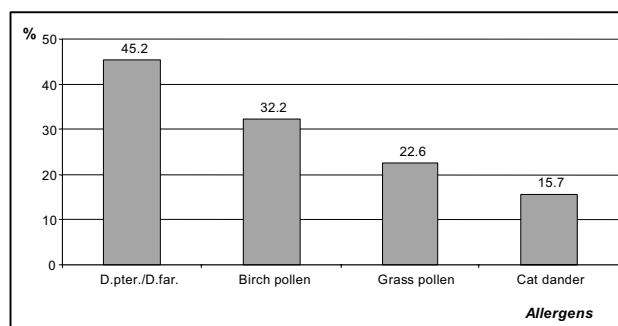


Figure 1. Incidence of positive APT for the study aeroallergens in patients with AD ($N = 115$).

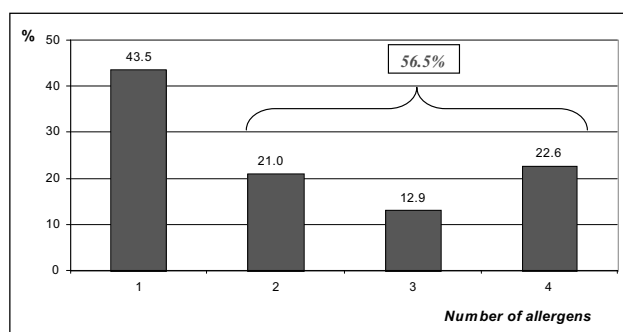


Figure 2. Incidence of positive APT for one, two, three or four study aeroallergens ($N = 62$).

Recent literature data point to the possibility of using APT in diagnostic work-up for AD [11, 16-18]. However, there is no uniform set of criteria regarding the testing techniques, and the results of such tests are not unequivocal [19, 20]. In order to increase allergen penetration, some authors have advocated removing superficial layers of epidermis by mechanical abrasion or adding contact irritants to test kits [21]. The resulting damage to the skin was supposed to facilitate penetration of the antigen into the skin, creating similar conditions to those resulting from *e.g.* scratching. This procedure increases the incidence of non-specific responses. This has led most authors to recommend performing APT on intact skin, which is considered to best emulate the conditions found in the environment of the patient [17, 19, 20]. Based on these recommendations, the technique employed in our study involved placing a solution of the allergen under occlusion on lesion-free intact skin.

Literature data differ also with respect to the form and concentration of allergens. Concentrations used vary from 1,000 to 10,000 PNU/g (protein nitrogen units) or 200 IR (biological units) [12-14, 22, 23]. It has also been established that white Vaseline is the most useful vehicle [24, 25]. Our study used kits supplied by Stallergenes (France) with allergens suspended in white Vaseline at a concentration of 200 IR. An exposure time of 48 hours is commonly accepted [12, 24, 26].

Another significant factor of APT finding evaluation is the time of its read-out, which is done after 48 and 72 hours. This results from the fact that the reaction shows a tendency to expire progressively with time [24], unlike reactions with non-protein allergens, which tend to accumulate progressively or have late reactions [9].

Intensification of APT reactions was evaluated according to the scale proposed by the European Task Force on Atopic Dermatitis (ETFAD) Consensus [13]. When compared with the evaluation of the usual patch test [9], the scale men-

tioned above had been expanded within the positive reaction intensification formulated by the number of papules within the reaction.

An analysis of the percentage of positive APT for aeroallergens in this study showed that the percentage of positive test results was 53.9% among AD patients and 6.2% among healthy volunteers, the difference being statistically significant at $P < 0.001$. Other authors report similar results, with contact hypersensitivity to aeroallergens detected in approximately 50% of AD patients [8, 18, 27]. In this study, hypersensitivity in the control group was limited to infrequent allergy to house dust mites. Other reports estimate the incidence of contact hypersensitivity to house dust mite allergens in a control group at 0-15% [12, 23, 25, 28]. Seidenari *et al.* [29] indicate that a positive result in a healthy volunteer can be of prognostic value, indicating a tendency to develop eczema in the future and/or suggesting a so-called "atopic diathesis".

The most common type of hypersensitivity in the study group was an allergy to the mixture of house dust mites (45.2%), which confirms the observations of others (39-45%) [12, 23]. There was a similar correspondence between our and literature data for APT testing for grass pollen and cat dander allergen, while the frequency of contact hypersensitivity to birch pollen in our study (32.2%) was twice as high as that reported by Darsow *et al.* (15.8%) [12]. This difference may be due to the abundance of this tree in the patients' environment. Since the same can be said about other aeroallergens, this emphasises the need to use different aeroallergen test kits in different regions of the world [30].

Our results show that 52.5% of patients who tested positive on APT had polyvalent hypersensitivity, usually to 2 or 4 allergen groups. In their study using house dust mites, cat dander and a mixture of grass pollen, Darsow *et al.* [24] found polyvalent hypersensitivity in a similar percentage of patients, with most subjects demonstrating hypersensitivity to 2 allergens.

The diagnostic utility of allergy tests depends on their sensitivity and specificity. On the basis of history data suggesting AD flare-ups following exposure to the study aeroallergens, the sensitivity of APT was established at 18.5-66.6% and specificity at 75.9-85.7% for various allergens. Our results corroborate the findings of other authors, who revealed a higher specificity and a lower sensitivity of atopy patch tests for aeroallergens [12, 13]. As in the case of patch tests, there is a possibility of false-positive reactions caused by irritant reactions, which do not differ clinically from allergic reactions [9]. This proves APT results should be considered together with the findings of other allergological tests, including history.

Table 1. Sensitivity and specificity of atopy patch tests for aeroallergens in patients with atopic dermatitis ($N = 115$)

Allergen	WD		FN		WN		FD		Sensitivity	Specificity
	Number	%	Number	%	Number	%	Number	%	%	%
D.pter./D.far.	42	36.5	21	18.3	42	36.5	10	8.7	66.6	80.7
Birch pollen	22	19.2	31	26.9	47	40.9	15	13.0	41.6	75.9
Grass pollen	16	13.9	37	32.2	52	45.2	10	8.7	30.1	83.8
Cat dander	7	6.1	31	26.9	66	57.4	11	9.6	18.5	85.7

WD : positive history of exacerbations of skin lesions following exposure to the aeroallergen and a positive APT for this allergen. FN : positive history of exacerbations, negative APT. WN : negative history of exacerbations, negative APT. FD : negative history of exacerbations, positive APT.

A comparison of our data on the frequency of positive APT for aeroallergens and the test's sensitivity and specificity in this study with literature data on SPT and elevated levels of sIgE specific to these allergens reveals some similarities as well as differences. Positive SPT and/or elevated sIgE levels are seen in AD patients 30% more frequently than positive APT results [3, 4]. This higher incidence of positive SPT and/or elevated sIgE levels can be explained by the frequent finding of concomitant allergic rhinitis and/or atopic asthma in these patients [31], since no correlation has been found between positive APT testing for aeroallergens and atopic respiratory conditions [19, 32].

Literature data stress the polyvalent nature of aeroallergen hypersensitivity determined by SPT and/or sIgE levels [3, 4] and our study of the APT method has led to the same conclusion. It has also been proved that SPT findings in AD patients and sIgE levels directed against aeroallergens are characterized by a higher sensitivity and a lower specificity [12, 13].

In conclusion, our study revealed that:

1. atopy patch tests, which are characterised by considerable specificity, confirm the role of polyvalent contact hypersensitivity to aeroallergens in the development of atopic dermatitis ;
2. positive aeroallergen ATP results are observed in the majority of patients and can thus be regarded as an additional diagnostic criterion in atopic dermatitis. ■

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