Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2013;22:39-42
doi: 10.2478/v10162-012-0030-3

Atopy patch testing with airborne allergens

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Abstract

Introduction: Atopy patch tests (APT) represent a relatively new diagnostic method for identifying the role of airborne allergens in atopic dermatitis flares. This study evaluates the role of airborne allergens in atopic dermatitis flares in a group of adult patients with atopic dermatitis. The primary goal was to detect the frequency of sensitization to these allergens in a group of patients with atopic dermatitis by APT. The secondary goal was to compare the results of APT with specific IgE against the same airborne allergens with regard to sensitivity and specificity.
Methods: Between November 2004 and October 2011, a cohort of 125 patients (37 males and 88 females) with atopic dermatitis was investigated using APT at the 1st Depatment of Dermatovenereology of the St. Anne Faculty in Brno, Czech Republic.
Results: In 36 (28.8%) patients, the APT were positive, and in 89 (71.2%) negative. The most common allergens were house dust mite allergens (12.8%), followed by grass and plant pollen (10.4%) and dog allergens (8%).
Conclusion: The results indicate that APT is a helpful tool for identifying airborne allergens as triggering factors of atopic dermatitis.

Received: 9 January 2013 | **Returned for modification:** 28 January 2013 | **Accepted:** 3 March 2013

Introduction

Some patients with atopic dermatitis (AD) have flares of their disease after contact with certain airborne allergens (1). The affected areas include the head and neck region and other sites not covered by clothes (Figure 1) – that is, an airborne distribution of atopic dermatitis (2). The most important airborne allergens are house dust mites, grass and tree pollen, animal dander, and molds (3). House dust mites are small arthropods similar to ticks. Their size is only about 0.3 mm and therefore they are invisible to the human eye. They are present in bed linen and mattresses and they feed on human keratin. The major antigens are glycoproteins of the bodies and feces of the mite Dermatophagoides pteronyssinus (Der p 1 and Der p 2). Antigens of the mite Dermatophagoides farinae (Der f 1 and Der f 2) are also important aeroallergens (3). In terms of the pollen, tree pollen dominates in the spring, grass pollen in the summer, and weed pollen in the fall (4). Cat allergens are contained in cat saliva and urine (4). These allergens are able to persist in the home environment up to 6 months after the removal of cats. Dog allergens derive from saliva, epithelia, and urine (4). Allergens in the urine of small rodents such as hamsters, guinea pigs, mice, and rats often sensitize children in particular (4). Molds are present in both the indoor and outdoor environment. The most important molds from the allergy point of view are Alternaria, Cladosporium, Aspergillus, Fusarium, and Botrytis (4).

It has been proven many times that in some patients with atopic dermatitis the disease can be induced by the direct application of airborne allergens to the skin (1, 5–7).

The pioneers of atopy patch testing with airborne allergens were Rostenberg and Sulzberger (8), who published the first studies as early as 1937. The renaissance of these tests appeared in 1982 as a result of studies conducted by Mitchell et al. (9). For this procedure, Ring et al. proposed the term atopy patch test (APT) (1). The principle of APT is almost the same as in traditional patch tests. It is the exposure of a small area of the skin to a suspected allergen in a certain concentration (the "allergy concentration") in a certain vehicle and for a certain period of time. Many researchers conducted APT in large groups of atopic patients in order to standardize these tests in terms of the vehicle, concentration, time of exposure, and so on (10–20). Practically all patients with atopic dermatitis–especially those with the air-exposed eczema pattern and those that observe AD flares after contact with airborne allergens–are suitable for atopy patch testing. The European task force on atopic dermatitis (ETFAD) proposed guidelines for atopy patch testing in 2006 (21, 22).

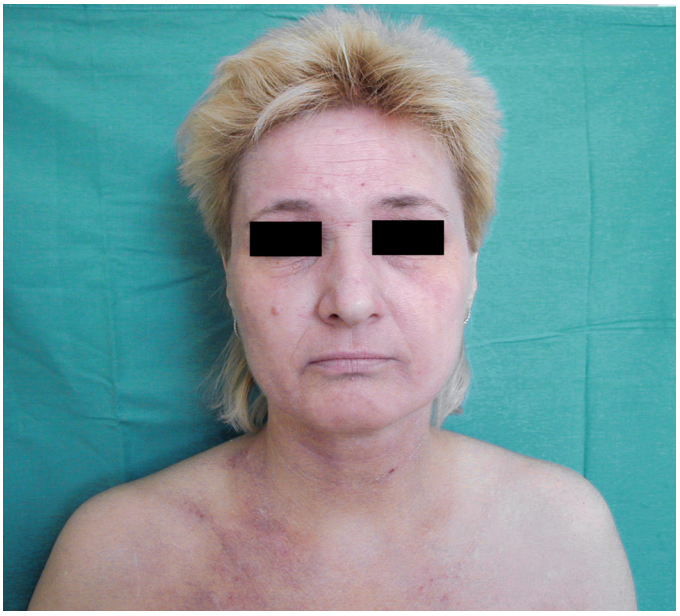

Figure 1 | Airborne distribution of atopic dermatitis.

Materials and Methods

Between November 2004 and October 2011, a total of 125 patients (37 males and 88 females) with atopic dermatitis were enrolled in the study. The average age of the patients was 28.4 years, ranging from 16 to 64 years. The demographic data of the cohort are

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presented in Table 1. Sixty-one patients had a mild form of atopic dermatitis, 44 had moderate atopic dermatitis, and 20 had a severe form of the disease. Fifty-five patients had atopic dermatitis in the head and neck region, 25 had only the eyelids affected, 23 had widespread dermatitis, and 22 patients had their atopic dermatitis in another location (e.g., flexures, hands, etc.). In addition to atopic dermatitis, 72 patients also had allergic rhinitis, 38 had allergic conjunctivitis, and 12 had asthma. Forty patients had no associated atopic disease except atopic dermatitis. In all patients, the level of total IgE was investigated. Eighty-nine patients had an elevated total level of IgE antibodies (above 150 IU/ml) whereas 36 patients had a normal IgE level.

Table 1 | Demographic data of the cohort of patients. P/N = positive/negative, Y/N = yes/no.

Gender	Number	Mean age (years)	Family history of AD P/N	Other atopic diseases Y/N
Male	37	29.6	18/19	22/15
Female	88	27.9	49/39	63/25
Total	125	28.4	67/58	85/40

In all of the patients, atopy patch tests were performed using Soluprick allergens from the ALK-Abelló company. A solution of histamine hydrochloride in a concentration of 10 mg/ml was used as a positive control and saline solution as a negative control. The allergens were applied to the patients' backs during the remission of atopic dermatitis (Figure 2). The first reading was made after 48 hours, the second after 72 hours, and the third after 96 hours. The evaluation of the reactions was made according to the ETFAD group recommendations. Antihistamines were discontinued at least 5 days prior to atopy patch testing, as were topical corticosteroids and topical immunomodulators. Systemic corticosteroids and immunosuppressive drugs were not allowed. APT were not conducted during the flares of atopic dermatitis. The level of specific IgE antibodies against airborne allergens (the same spectrum as used for APT) was also evaluated in every patient. The investigation was conducted in the immunological laboratory using the chemiluminescence method on an Immulite 2000 analyzer (Siemens company).

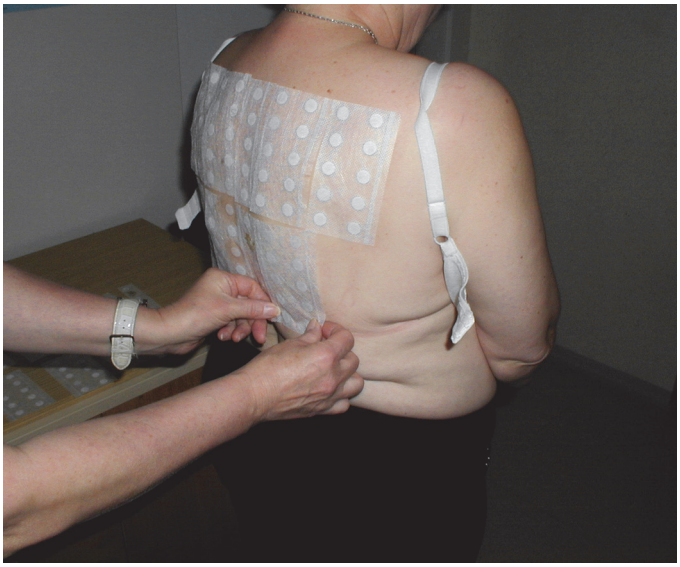

Figure 2 | Application of atopy patch tests.

Results

The atopy patch tests were positive in 36 of 125 patients tested (28.8%). Of these 36 positive patients, 17 had a positive reaction to only one airborne allergen and 19 to more than one airborne allergen. The APT were negative in 88 patients. These data are summarized in Table 3.

Table 2 | Distribution of atopic dermatitis (AD) lesions in patients.

Distribution of AD	n	%
Head and neck	55	44
Eyelids only	25	20
Widespread	23	18.4
Elsewhere/flexures etc.	22	17.6
Total	125	100

Table 3 | Overall results of atopy patch tests (APT). n = number of patients.

APT	Result	Number of allergens	n
	Positive	› 1	19
		1	17
	Negative	89	

The frequency of sensitization to airborne allergens is shown in Table 4. The most common allergy was found to *Dermatophagoides pteronyssinus* (10.4%), followed by birch tree pollen and dog epithelia (both 8%).

Table 4 | Frequency of sensitization to airborne allergens. n = number of positive reactions in APT.

	Allergen	n	%
1.	Grey alder	6	4.8
2.	Birch tree	10	8
3.	Cobnut tree	7	5.6
4.	*Dermatophagoides farinae*	8	7
5.	*Dermatophagoides pteronyssinus*	13	10.4
6.	*Alternaria alternata*	4	3.2
7.	*Aspergillus fumigatus*	2	0.8
8.	Meadow oat	8	7
9.	Cocksfoot	8	7
10.	Fescue grass	4	3.2
11.	Rye grass	4	3.2
12.	Timothy grass	6	4.8
13.	Blue grass	2	0.8
14.	Absinthe	8	7
15.	Dog epithelia	10	8
16.	Cat epithelia	6	4.8
17.	Horse epithelia	4	3.2

The frequency of sensitization to groups of allergens is shown in Table 5. The most common allergens were house dust mite allergens (12.8%), followed by grass and plant pollen (10.4%) and dog allergens (8%). In a subgroup of patients with a positive history of AD flares after contact with airborne allergens, the frequency of positive APT was higher (44.7%) compared to the subgroup of patients with a negative history (21.8%); see also Table 6.

Table 5 | Frequency of sensitization to groups of airborne allergens. n = number of positive reactions in APT.

	Allergen	n	%
1.	House dust mites	16	12.8
2.	Grass and plant pollen	13	10.4
3.	Dog epithelia	10	8
4.	Tree pollen	8	6.4
5.	Cat epithelia	55	44
6.	Horse epithelia	4	3.2

Table 6 | Results of APT in subgroups according to patient history. n = number of patients, APT+ = number of patients with positive APT, APT– = number of patients with negative APT, % = percentage of positive APT results in a given subgroup.

Patient history	n	APT+	APT–	%
Positive	38	17	21	44.7
Negative	87	19	68	21.8

In the subgroup of patients living in an urban area the percentage of positive APT was slightly higher (30.1%) than in patients living in a rural area (APT positive in 26.2%); the most frequent allergen in the first subgroup was *Dermatophagoides pteronyssinus* (14.5%), whereas in the second subgroup it was grass pollen (14.3%); see Table 7.

Table 7 | Results of APT according to the area of residence of patients. n = number of patients, APT+ = number of patients with positive APT, APT– = number of patients with negative APT, % = percentage of positive APT results in a given subgroup, D. pteron. = *Dermatophagoides pteronyssinus*.

Residence	n	APT+	APT–	%	Most common allergen
Urban area	83	25	58	30.1	D. pteron.
Rural area	42	11	31	26.2	Grass pollen

Eighty-three patients had a positive specific IgE to at least one airborne allergen and 42 patients had a negative specific IgE to all airborne allergens tested. The sensitivity of the APT in relation to the patients' history was 41.3% and the specificity was 77.4%. The sensitivity of the specific IgE results in relation to the patients' history was 80.1% and the specificity 30.9% (Table 8).

Table 8 | Sensitivity and specificity of APT and specific IgE results.

	APT	Specific IgE
Sensitivity	41.3%	80.1%
Specificity	77.4%	30.9%

Discussion

In the last two decades, many groups have performed and studied the APT (10–20). It has been proven that at the molecular level airborne allergens come in contact with the skin of the atopic person, penetrate through the skin barrier, and are phagocyted by dendritic cells (mostly Langerhans cells, LC), where the antigen is internalized and processed. These cells then migrate to the regional lymph node, where they present the antigen to naive Th cells. In the case of sensitization, the naive Th cells differentiate into Th2 cells, which produce cytokines–especially IL-4, which stimulate B lymphocytes to produce specific IgE directed against the causative allergen. These IgE molecules are able to bind on the surface of Langerhans cells mostly via the high affinity receptor for IGE (FcεRI) and wait there for another contact with the same allergen (23). A specific clone of T lymphocytes is also activated during the elicitation phase (24). These memory cells exprime CLA (cutaneous lymphocyte associated), whose ligand is E-selectin on endothelial cells, enabling the homing of these memory cells in the skin (23). After repeated contact with the specific allergen (including atopy patch tests), this allergen is trapped by Langerhans cell and binds to the specific IgE on their surface. Through the release of specific cytokines from LC, the homing T lymphocytes are activated very rapidly because they are ready on site (in the skin) and they activate B cells with subsequent overproduction of IgE binding not only to LC but also to mastocytes and basophils, leading to the release of histamine, prostaglandins, and leukotrienes (early phase reaction) 15 to 60 minutes after contact with airborne allergens. Activated Th cells then produce IL-5, which attracts eosinophils producing a major basic protein, eosinophil-derived neurotoxin, and eosinophilic cationic protein (24). These proteins, together with pro-inflammatory cytokines produced by monocytes and cytotoxic T lymphocytes, lead to inflammation of the epidermis and upper dermis, clinically presenting as the flare of atopic dermatitis or positive reaction in APT (late phase reaction) 24 to 48 hours after the contact with airborne allergens. Whereas in the first 24 hours IL-4-positive CD4+ cells predominate, in the next 24 hours the IFNy-positive CD4+ cells take over, and so the response is biphasic (26).

The percentage of positive reactions in APT in patients with atopic dermatitis in the studies dealing with this type of testing ranged from 15 to 100% (21). In a large multicenter study in Germany (14), in more than 280 patients house dust mite was found to be the most common positive reaction (44%), followed by grass pollen (23.8%), cat epithelium (15%), birch pollen (16.7%), and mugwort pollen (5%). Most of the patients were sensitized to only one allergen, and rarely to two or three allergens. In another large randomized multicentric trial conducted in a set of 314 adults with atopic dermatitis, the sensitization to Dermatophagoides pteronyssinus was 39%, to birch pollen 17%, to grass pollen 15%, and to cat epithelia 10% (22). Darsow et al. reported the most frequent allergen-eliciting positive reaction from Dermatophagoides pteronyssinus (36.1%), followed by cat dander (22%) and grass pollen (16.7%) (11). In a study conducted in Croatia by Kuljanac et al., the most frequent allergy in APT was also found to be Dermatophagoides pteronyssinus and the authors conclude that APT may identify the triggering factor in atopic dermatitis patients (27). In the patients in this study, the most common sensitization was detected to Dermatophagoides pteronyssinus (10.4%), followed by birch tree pollen and dog epithelia (both 8%). In terms of the groups of allergens, the most common were positive reactions to house dust mite allergens (12.8%), followed by grass and plant pollen (10.4%) and dog allergens (8%).

It is obvious that positive APT reactions are much more frequent in patients with a specific history of eczema flare after airborne allergen contact. In the multicenter study mentioned above, the positivity of APT was significantly higher in the subgroup of patients with exacerbations of the AD during the summer season (14). Ring et al. found the rate of positive APT to be significantly higher in the subgroup of patients with the airborne exposure distribution of atopic eczema (69%) versus the subgroup of patients with AD in other locations (39%) (1). Clark and Adinoff also found that only airborne allergens identified by history or in the homes of patients with AD elicited a positive reaction in APT (18). In a trial conducted by Reitamo et al., three-quarters of patients with spring-season exacerbations of atopic dermatitis had positive APT (19). In these patients, the APT were also more frequently positive (44.7%) in a subgroup of patients with a history of flares of AD after contact with airborne allergens than in the subgroup with a negative history (21.8%).

Most authors confirm that the sensitivity of specific IgE (and prick tests) is relatively high, whereas the specificity is lower. On the other hand, APT have higher specificity and lower sensitivity (14, 22). In the study by Samochocky et al., the sensitivity of APT in relation to the history of patients varied between 18 and 66% according to the allergen, and the specificity exceeded 75% (28). Wistokat found a sensitivity of APT between 45 and 71% according to the aller-

gen and a specificity between 76 and 95% (29). According to Wistokat, the specificity was significantly higher than in prick tests (27.3 to 54%) and specific IgE (31.8 to 61.9%) (28). In the Darsow study of 314 patients with atopic dermatitis, the sensitivity of APT in relation to patient history was 67 to 75% and the specificity was 84 to 90%. The sensitivity of prick tests in relation to patient history was 100% and the sensitivity of specific IgE was 92%. The specificity in relation to patient history was 33% both for prick tests and specific IgE (22). In this study, the sensitivity of the APT in relation to patient history was 41.3% and the specificity was 77.4%. The sensitivity of the specific IgE in relation to patient history was 80.1% and the specificity was 30.9%. This makes it possible to conclude that specific IgE (and presumably also prick tests) have higher sensitivity: they are able to identify a wider spectrum of airborne allergens that might be involved in flares of AD, but they might also be associated with other atopic symptoms such as allergic rhinitis, conjunctivitis, or allergic asthma. On the other hand, the high specificity of APT means that these tests are more specific; that is, they can be more precise than the results of specific IgE (and prick tests). Therefore it seems that APT may provide further diagnostic information in addition to prick tests or specific IgE results and that it is advantageous to combine these methods when identifying the airborne allergens as a possible cause of the flares of AD in a given patient.

Thus the value of APT in clinical practice lies in the fact that on the basis of the results of APT one should be better able to select patients that might benefit from avoidance measures and possible from specific immunotherapy with airborne allergens.

On the other hand, APT are rather time-consuming and need a skilled dermatologist to conduct and evaluate, and so they should be reserved for specialized dermatology allergy offices within tertiary referral dermatology centers.

Conclusions

This study's results confirm that atopy patch tests, as a direct challenge with airborne allergens, are able to elicit a positive reaction in sensitized patients with atopic dermatitis. This method is suitable for identifying airborne allergens as possible triggering factors of atopic dermatitis. In comparison to current methods such as prick tests and specific IgE, APT has certain benefits: it correlates more closely with patients' history regarding AD flares than prick tests or specific IgE. Moreover the APT results are more specific for atopic dermatitis.

Atopy patch tests therefore extend the diagnostic armamentarium in the identification of airborne allergens as triggering factors of atopic dermatitis. The identification of airborne allergens as triggering factors of atopic eczema is important for preventive measures and when considering a specific immunotherapy.

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