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Atopy patch tests with aeroallergens in children aged 0–3 years with atopic dermatitis

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Key words: aeroallergens; atopic dermatitis; atopy patch test; children; urticaria.

Sensitization to aeroallergens, commonly associated with direct type, IgE-mediated allergy, is a common finding

in both pediatric and adults patients with atopic dermatitis (AD). The exact role of this sensitization in the pathogenesis of AD remains controversial. There does seem to be a subgroup of patients with AD where contact with aeroallergens, such as house dust mite (HDM) or grass pollen, is capable of worsening eczematous skin lesions (1). Adequate avoidance measures may be helpful in controlling AD in these patients, although results from clinical trials are contradictory (2–4).

Additional evidence for a possible role of aeroallergens in the pathogenesis of

AD is found in the fact that epicutaneous application of these allergens can elicit delayed type, eczematous skin reactions in patients with AD (5, 6). This so-called atopy patch test (APT) was first described in 1982 and has been the focus of increased research interest over the last 10–15 years (7). The APT is currently widely accepted as an *in vivo* model of AD (8). However, differences in methodology and the lack of a golden standard for the presence of a relevant sensitization to aeroallergens in AD are two major obstacles in the development of the APT as an addition to our allergologic work-up in patients with AD (7, 9).

Most of the current clinical data on the APT with aeroallergens are based on adult patient populations and pediatric data are scarce. We initiated a prospective clinical study in children with AD aged up to 3 years, to evaluate the presence of positive APT reactions and their correlation with elevated levels of serum specific IgE and/or the presence of positive skin prick test (SPT) reactions.

The study was performed at the pediatric dermatology out-patient clinic of the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands. Children below the age of 3 years with AD and with an indication for an allergologic work-up, were eligible for inclusion. AD was defined by the criteria of Williams et al. (10). Indications for an allergologic work-up consisted of refractory skin disease or suspected allergy to aero- or food allergens because of reported reactions after exposure or the presence of pre-existing diets. The inclusion period lasted 2 years and 10 months. All patients were subjected to a careful history of possible allergic symptoms combined with measurement of serum specific IgE and the APT. Additional SPT was performed only in children aged > 1 year. Investigated allergens included dog dander, cat dander and HDM. Allergens for the SPT and APT were obtained from ALK-Abello (Nieuwegein, the Netherlands) and consisted of aqueous solutions with an allergen concentration of 10 000 PNU. Severity of AD at the time of the skin tests was measured using the objective SCORAD (11).

Atopy patch test was performed on the unabrased skin of the back using normal (8 mm) Finn-chambers on scanpor®

(Epitest Ltd Oy, Tuusula, Finland). The buffer solution was tested as a negative control. After 20–30 min, the test areas were examined to exclude urticarial weal and flare reactions, in which case the skin test would be removed. Subsequently, the test chambers were covered with fixomull® to prevent them from shifting. After 48 h, the test chambers were removed. Evaluation of the skin tests took place after 48 and 72 h using the guidelines described by the European Taskforce on Atopic Dermatitis (ETFAD) (12). Clear-cut reactions of 2+ or more were regarded as positive. Urticarial reactions were also included as positive, immediate type APT reactions.

Blood was drawn from each patient. Allergen-specific IgE was measured in serum with the CAP system (Pharmacia, Woerden, The Netherlands) according to the manufacturer's instructions. Only levels of 0.70 U/l, or above were regarded as positive.

A drop of the solution was applied on the volar surface of the forearm, after which a lancet was used to penetrate the skin through the drop. Histamine was tested as a positive control. The results were evaluated by measuring the mean diameter of the wheal reaction after 15 and 30 min. A positive reaction consisted of a wheal, which had a mean diameter of at least 3 mm and was at least half the diameter of the positive control.

The study was approved by the Medical Ethics Committee of the Erasmus MC, Rotterdam, the Netherlands. The parents of all patients signed informed consent. The statistical analysis was performed using SPSS version 11.0. Statistical analysis was performed in patients with complete data necessary for the calculations. Because of missing test results in some patients, the *n*-value varies between statistical calculations. There was no suspicion that missing data occurred selectively and we could not detect a bias in patient characteristics such as age, sex or severity of AD. The kappa (κ) statistic was used for quantifying and testing agreement between the various test scores. The strength of agreement is interpreted as described by Landis and Koch (13).

One hundred and forty-eight children were eligible for inclusion. We experienced 13 dropouts because of active skin disease on the test areas (*n* = 8), very

Table 1. Frequency and percentages of positive and negative atopy patch test (APT) results

	APT positive	APT negative
	Frequency (%)	Frequency (%)
Dog (<i>n</i> = 120)	15 (12.5)	105 (87.5)
HDM (<i>n</i> = 122)	30 (25)	92 (75)
Cat (<i>n</i> = 124)	27 (22)	97 (78)

Results are shown for the three different aeroallergens: dog dander, house dust mite (HDM) and cat dander.

strong positive dermatography (*n* = 1), multiple positive APT reactions, including the negative control (angry back, *n* = 3) and one child developed fever caused by an airway infection during the test week. This left 135 children included, with an age distribution ranging from 5 to 35 months and a mean age of 20 months with a SD of 9 months. The mean objective SCORAD score was 13.6 with a SD of 8.3. There were 51 (38%) girls and 84 (62.2%) boys. SPT was performed only in children aged above 1 year (*n* = 102/135).

Table 1 lists the number and percentages of positive and negative APT results for the three different aeroallergens. The majority of positive APT reactions consisted of classical delayed type eczematous reactions. However, immediate type, urticarial reactions were seen in four of 15 (27%) of the tests with dog dander, four of 30 (13%) of the tests with HDM and six of 27 (22%) of the tests with cat dander. All patients with immediate type, urticarial reactions showed elevated levels of specific IgE and/or a positive SPT reaction.

Sensitization to more than one allergen was found in the APT as well as in measurement of specific IgE and the SPT. Details are listed in Table 2. All patients with more than one positive APT reaction showed consistency in the type of APT reaction. They either had immediate type urticarial reactions or delayed type eczematous reactions. We did not find any patient with both reaction types.

The agreement between different tests is detailed in Table 3. The κ -tests showed statistically significant agreement between all three pairs of tests, although the strength of agreement varied between

Table 2. Frequency and percentages of patients with positive reactions to 0, 1, 2 or 3 of the aeroallergens in the atopy patch test (APT), serum specific IgE measurement or skin prick test (SPT), respectively

No.	APT positive (<i>n</i> = 116)	IgE positive (<i>n</i> = 123)	SPT positive (<i>n</i> = 104)
0	70 (60.3)	72 (58.5)	64 (61.5)
1	28 (24.1)	22 (17.9)	17 (16.3)
2	14 (12.1)	23 (18.7)	18 (17.3)
3	4 (3.4)	6 (4.9)	5 (4.8)

Values within parenthesis are expressed in percentage.

Table 3. Agreement between the atopy patch test (APT), serum specific IgE measurement and skin prick test (SPT) as was calculated using the κ -test

		Strength of <i>n</i> agreement	κ -value	<i>P</i> -value
<i>APT vs IgE</i>				
Dog	115	Fair	0.27	0.005
HDM	119	Fair	0.38	<0.0005
Cat	120	Fair	0.38	<0.0005
<i>APT vs SPT</i>				
Dog	93	Moderate	0.53	<0.0005
HDM	95	Fair	0.31	0.003
Cat	97	Fair	0.39	<0.0005
<i>SPT vs IgE</i>				
Dog	98	Moderate	0.5	<0.0005
HDM	101	Substantial	0.77	<0.0005
Cat	99	Moderate	0.57	<0.0005

Results are shown for the three different aeroallergens: dog dander, house dust mite (HDM) and cat dander.

fair and substantial. We did not find any statistically significant impact on the data described above by either sex or age.

Our study was performed using dog dander, cat dander and HDM as common indoor aeroallergens. We found clear-cut positive APT reactions in respectively 12.5%, 22% and 25% of our patient population. Positive APT reactions to HDM were the most frequent, which is in concordance with earlier literature on adult patients (6, 9). The frequency of positive APT to HDM seems to be higher in adult patients with reported frequencies around 40% (6, 9). In contrast, we seem to find more positive APT to cat

dander in our patient population compared to the reported frequencies of 10–15% in adult patients (6, 9).

In our patient population, there was a statistically significant but only fair agreement between the APT and the presence of specific IgE or the SPT. Positive delayed type APT reactions were also found in patients without specific IgE or positive SPT, suggesting that positive APT reactions may be facilitated by specific IgE but are not dependent on its presence. This is in concordance with the current understanding of the pathogenesis of the APT (7, 8). Unlike a recent publication from Möhrenschrager et al. (14), we did not find any differences in APT, serum specific IgE and SPT reactivity between boys and girls. There were also no detectable differences between these parameters when we divided our patients into different age groups. We could not find a correlation between the presence of positive APT reactions and the objective SCORAD at the time of the skin tests (data not shown). As there is no gold standard for the diagnosis of a relevant allergy to aeroallergens in patients with AD, we did not attempt any conclusions with regard to the clinical relevance of the positive APT reactions.

We found a relatively high number (13–27%) of immediate type, urticarial APT reactions in our patient population. These urticarial reactions were only found in patients with elevated serum levels of specific IgE and/or positive SPTs against the allergen tested. Several test sites with urticarial reactions showed clear-cut delayed type, eczematous reactions after 48 and 72 h, even though the skin test itself was removed after 20–30 min (A.C.A. Devillers, F.B. de Waard-van der Spek, A.P. Oranje, pers. obs.). Our relatively young patient population may be largely responsible for the relatively high percentage of urticarial reactions (15). One hypothesis could be that allergens are able to penetrate the epidermis of young children with AD more readily than in adults with AD. However, we believe that there might also be an underreporting of immediate type, urticarial APT reactions in the current literature.

Unfortunately, as is often the case in studies on the APT, our study methodology is not completely comparable to the above cited adult studies. Next to the

age difference of the patient populations, the most obvious difference is in the allergen preparations that were used. From a practical point of view, we chose to use the same aqueous allergen solutions for the SPT as well as the APT, whereas petrolatum-based allergen preparations were used in most recent adult studies. Based on current knowledge, these petrolatum-based preparations are preferable for further standardization of the APT (8). Despite this reservation, we believe the data described above add valuable information to our current knowledge of the APT with aeroallergens in children.

In conclusion, we found a substantial number of clear-cut positive APT reactions to three common aeroallergens, with a relatively high percentage of urticarial reactions, in our patient population of young children with AD. Although the APT seems promising as a diagnostic and possibly even prognostic skin test, its clinical value still appears limited at the moment (8, 16). Further studies aimed at standardization, reproducibility and clinical validation in children as well as adults are needed before the APT with aeroallergens can be used in routine daily clinical practice (8). For future use, we would like to prompt increased interest in the immediate type urticarial reactions in the APT, especially in children.

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Occupational asthma caused by chamomile

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Key words: *Asteraceae*; asthma; bronchoprovocation tests; chamomile; occupational disease.

Chamomile flower (*Matricaria chamomilla* L. or *recutita*

L., botanical family of *Asteraceae* or *Compositae*) is widely used as a medicinal agent because of its sedative and anti-inflammatory properties. Immunoglobulin E-mediated urticaria and anaphylaxis have been reported following topical application (1), ingestion of herbal tea (2), and administration of chamomile-containing enema (3). Herein, we describe a tea-packing plant worker who developed occupational asthma and rhinitis caused by inhalation exposure to chamomile dust.

A 43-year-old man developed work-related rhinoconjunctivitis and asthma

Inhalation of chamomile dust can cause IgE-mediated rhinitis and asthma among herbal tea workers.