
Relationship between the atopy patch test and clinical expression of the disease in children with atopic eczema/dermatitis syndrome and respiratory symptoms

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Background: The atopy patch test (APT) may be the only positive skin test result in patients with either atopic eczema/dermatitis syndrome (AEDS) or respiratory abnormalities with or without AEDS.

Objective: To investigate the possible significance of APT to dust mite by comparing the positive result to this test with that of the skin prick test (SPT) in patients with different characteristics.

Methods: A total of 297 individuals (178 boys and 119 girls) aged 5 to 221 months (mean [SD] age, 64.5 [42.1] months; median age, 58 months) were included in this study. Participants were divided into 4 groups: current AEDS, current AEDS and respiratory symptoms, past AEDS and respiratory symptoms, and respiratory symptoms with neither current nor past AEDS (control group). All the patients underwent SPT and APT using house dust mite extract.

Results: In the study groups, the rate of positivity was significantly higher for APT, whereas in the control group, there were significantly more positive results to SPT ($P < .001$ for both). Multivariate analysis showed that there was a high probability of a positive APT result in patients with AEDS (odds ratio [OR], 17.4), with AEDS and respiratory disease (OR, 21.9), and with past AEDS and respiratory disease (OR, 22.8).

Conclusions: These patients with AEDS showed 2 different patterns of allergic response to allergens, one IgE mediated (as evaluated by positive SPT results) and the other cell mediated (as evaluated by positive APT results). The former seems to follow the so-called atopic march model, and the latter persists even after the disappearance of AEDS and is likely to be implicated in the pathogenesis of respiratory allergy.

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INTRODUCTION

Atopic diseases are generally diagnosed by performing skin prick tests (SPTs) or by measuring specific IgE antibodies to environmental allergens. The atopy patch test (APT), which consists of applying the suspected allergen to the skin using the same method of patch testing used for contact dermatitis, was introduced in 1989 as a technique to evaluate sensitization to aeroallergens in individuals with atopic eczema/dermatitis syndrome (AEDS).¹ A variety of subsequent studies^{2–7} confirmed the ability of the APT to detect such sensitization, particularly to house dust mites. Likewise, foodstuffs are potential triggers of AEDS that can be tested using the APT, but this testing technique has not yet been standardized. A recent multicenter European study⁸ evaluated the importance of APT in 314 patients with AEDS in remission using inhal-

ant and food allergen extracts and found a prevalence of positive APT results up to 57%. A 17% positive result rate to APT in the presence of a negative SPT result was recorded, which suggests that many patients may be diagnosed as having an allergy based exclusively on the results of APT. This is consistent with a previous study⁹ that demonstrated that the APT result is often positive in patients with respiratory allergy and negative SPT results. We investigated the possible significance of APT to dust mite by comparing its positive result with that of SPT in patients with different characteristics.

MATERIALS AND METHODS

Participants

A total of 297 patients (178 boys and 119 girls) aged 5 to 221 months (mean [SD] age, 64.5 [42.1] months; median age, 58 months) were included in this study. Of these patients, 248 (148 boys and 100 girls) aged 5 to 221 months (mean [SD] age, 61.9 [43.2] months; median age, 53 months) had a positive history of AEDS and were divided into 3 groups: current AEDS, current AEDS with respiratory symptoms, and past AEDS with respiratory symptoms. Forty-nine patients with rhinosinusitis or asthma but without AEDS (30 boys and

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19 girls) aged 36 to 163 months (mean [SD] age, 77.7 [33.1] months; median age, 78 months) served as the control group.

METHODS

The AEDS was diagnosed according to the criteria of Hanifin and Rajka,¹⁰ and rhinosinusitis was diagnosed on the basis of the position paper from the European Academy of Allergology and Clinical Immunology.¹¹ All the patients underwent SPT with inhalant allergen extracts (Stallerg enes, Antony, France), with test positivity evaluated according to the guidelines from the European Academy of Allergology and Clinical Immunology,¹² and APT using house dust mite extract (Merck, Milan, Italy). The material used for this test was composed of inert dust mite bodies purified to 20% (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, 1:1), with white petroleum jelly (Vaseline), 20%, and white mineral oil used as excipients. The substance to be tested was applied onto intact skin of the lower back and was held firmly in position using adhesive patch tests. These patch tests were made up of aluminum Finn chambers 8 mm in diameter, with an area of 50 mm² and a volume of approximately 20 µL. The application period was 48 hours. The test was read no less than 30 minutes after removal to avoid margin effect. Results were interpreted according to the American Academy of Dermatology for APT¹³ using a scale ranging from 1+ (weak reaction) to 3+ (very strong reaction). Only reactions of 2 and 3+ were considered positive for the purpose of this study.

Statistical Analysis

For continuous variables, the variation between groups was compared by means of analysis of variance, and the differences were analyzed using the χ^2 test, with dichotomized age by the median value. Contingency tables were used to analyze the association of each variable (sex, age, and positive family history) with the tests used in the study (SPT and APT). Determinants of the single pathologic diseases were evaluated by means of multivariate analysis, performed using logistic regression analysis. As dependent variables we used the pathologic condition of the study groups vs the control

group, the pathologic condition of the groups with past AEDS and respiratory symptoms or only respiratory symptoms vs the pathologic condition of the group with current AEDS and respiratory symptoms, and the pathologic condition of the group with only respiratory symptoms vs the pathologic condition of the group with past AEDS and respiratory symptoms. In each model, the percentage of distribution of sex, age, positive family history, and positivity of SPT and APT was used. Statistical significance was assumed for $P < .05$. All statistical analysis was performed using a software program (SPSS for Windows version 11.0; SPSS Inc, Chicago, Illinois). Results are expressed as mean or median (SD).

RESULTS

Case history data defined a family atopy in 168 individuals (67.7%), with no difference regarding sex. The 3 study groups and the control group were formed as described in Table 1. Sex had no effect on the kind of pathologic abnormality or results of diagnostic tests.

The overall rate of positivity was significantly higher for APT than for SPT ($P < .001$). According to age, SPT results were positive in 9 of the 125 patients (7.2%) 53 months and younger (median age) and in 23 of the 123 patients (18.7%) older than 53 months ($P = .001$). The APT result in these 2 age groups was positive in 101 (80.8%) and 94 (76.4%) patients, respectively. The positive outcome to APT was significantly more frequent than to SPT in children 53 months and younger ($P < .001$).

Table 2 reports the responses to SPT and APT to dust mite in the different groups: significantly more frequent positive results were found for APT in patients with AEDS ($P < .001$) and for SPT in the control group compared with the other groups ($P < .003$). In the control group, significantly higher positivity to SPT compared with APT was found ($P < .001$). In this group, only 6 subjects (4 with rhinosinusitis and 2 with asthma, all with positive SPT results) had positive APT results. In logistic regression, positivity to testing was predicted by group for APT ($P < .001$) and SPT ($P < .003$). Table 3 provides the differences observed between the study

Table 1. Demographic and Baseline Characteristics of the Different Groups^a

	Group A (n = 39)	Group B (n = 78)	Group C (n = 131)	Group D (n = 49)	P value
Sex, No. (%)					
M	27 (69)	45 (58)	76 (58)	30 (61)	.60
F	12 (31)	33 (42)	55 (42)	19 (39)	
Age, mo					
Mean (SD)	13.7 (10.9)	70.3 (40.6)	71.3 (41.4)	77.7 (33.1)	<.001
Median	11.0	63.5	59.0	78.0	
Range	5–61	14–221	14–206	34–163	
Categorized median age, No. (%)					
≤58 mo	38 (97)	34 (44)	64 (49)	17 (35)	.001
>58 mo	1 (3)	44 (56)	67 (51)	32 (65)	
Family history of atopy, No. (%)	25 (64)	52 (67)	91 (69)	23 (47)	.04

^a Group A consists of patients with current atopic eczema/dermatitis syndrome (AEDS); group B, patients with current AEDS and respiratory disease; group C, patients with past AEDS and respiratory disease; and group D, controls.

Table 2. SPT and APT Responses in the Different Groups^a

	Group A (n = 39)	Group B (n = 78)	Group C (n = 131)	Group D (n = 49)	P value
SPT positive to mites, No. (%)					
Overall	3 (8)	16 (21)	13 (10)	22 (45)	.003
Boys	3	10	9	13	
Girls	0	6	4	9	
APT positive to mites, No. (%)					
Overall	30 (77)	61 (78)	104 (79)	6 (12)	.001
Boys	20	34	65	5	
Girls	10	27	39	1	

Abbreviations: APT, atopy patch test; SPT, skin prick test.

^a Group A consists of patients with current atopic eczema/dermatitis syndrome (AEDS); group B, patients with current AEDS and respiratory disease; group C, patients with past AEDS and respiratory disease; and group D, controls.

Table 3. Positivities to SPT and APT in the Different Groups^a

Test or single determinant	Group comparison	Test positivity, %	χ^2	OR (95% CI)	P value
Univariate Analysis					
SPT	D vs A	44.9 vs 7.7	19.871	0.114 (0.051–0.256)	<.001
APT	D vs A	12.2 vs 76.9	32.704	27.605 (10.641–71.615)	<.001
SPT	D vs B	44.9 vs 20.5	6.187	0.157 (0.060–0.411)	.01
APT	D vs B	12.2 vs 78.2	33.471	23.889 (7.691–74.199)	<.001
SPT	D vs C	44.9 vs 9.9	16.606	0.263 (0.112–0.614)	<.001
APT	D vs C	12.2 vs 79.4	34.177	25.716 (9.373–70.550)	<.001
SPT	A vs C	7.7 vs 9.9	0.065	2.307 (1.299–4.096)	.80
APT	A vs C	76.9 vs 79.4	0.002	0.932 (0.470–1.847)	.97
SPT	B vs C	20.5 vs 9.9	2.554	1.677 (0.770–3.651)	.12
APT	B vs C	78.2 vs 79.4	0.001	1.076 (0.430–2.697)	.97
Multivariate Analysis					
Age ≤58 mo	Overall	NA	NA	29.3 (1.48–582)	.02
Age >58 mo	B vs A	NA	NA	0.026 (0.003–0.202)	<.001
	B vs D	NA	NA	0.03 (0.002–0.67)	.03
APT positive	Overall	NA	NA	21.9 (2.4–198.6)	.006
	A vs D	NA	NA	17.4 (6.4–47.3)	<.001
	B vs D	NA	NA	21.9 (2.42–198.6)	.006
	C vs D	NA	NA	22.8 (8–65)	<.001
SPT positive	A vs D	NA	NA	0.15 (0.58–3.81)	<.001
	C vs D	NA	NA	0.22 (0.08–0.62)	.004
	C vs A	NA	NA	2.13 (1.17–3.88)	.01

Abbreviations: APT, atopy patch test; CI, confidence interval; NA, not applicable; OR, odds ratio; SPT, skin prick test.

^a Group A consists of patients with current atopic eczema/dermatitis syndrome (AEDS); group B, patients with current AEDS and respiratory disease; group C, patients with past AEDS and respiratory disease; and group D, controls.

groups and the control group according to univariate and multivariate analysis.

DISCUSSION

This study indicates that results of APT with dust mite extract are more frequently positive than results of SPT in children with current or past AEDS regardless of the presence of respiratory allergy with rhinosinusitis or asthma. In particular, multivariate analysis showed high odds ratios (ORs) concerning the probability of having AEDS in patients with positive APT results (OR, 21.9) and of having a positive APT result in patients with AEDS (OR, 17.4). However, there was an even higher probability of a positive APT result in patients

with current AEDS and respiratory disease (OR, 21.9) and past AEDS and respiratory disease (OR, 22.8). This suggests that the mechanisms underlying skin response to the APT are related to the pathogenesis of AEDS, which is highly complex and increasingly investigated.^{14–18} The current knowledge on AEDS attributes a major role as pathobiologic factors to skin barrier dysfunction and to hyperreactivity and to exposure to immunologic stimuli, such as allergens and microbes.¹⁷ This interaction, in which dendritic cells seem to play a pivotal role,¹⁶ leads to a T-cell response in the skin initially of T_H2 type but later of T_H1 type and to a systemic T_H2 response, inducing the isotype switching to IgE synthesis and the involvement of eosinophils.¹⁸ The importance of the

systemic response is made evident by the natural history of the atopic disease, characterized by early presentation with AEDS and subsequent respiratory manifestations with asthma and rhinitis, summarized by the term *atopic march*.¹⁹

As far as the role of environmental allergens that enter through the skin is concerned, experimental studies²⁰ have demonstrated that the epicutaneous sensitization to protein antigens was associated with the development of airway hyperresponsiveness after inhalation of the same antigens. Regarding skin exposure to dust mite allergens, their application by the APT induced a T-cell response adherent to the aforementioned model with early T_H2 but late T_H1 dominance in the inflamed skin.¹⁵

In a study²¹ investigating in 32 patients with current AEDS the possible correlation between positive APT results and other immunologic variables, it was found that approximately half of the patients with specific IgE in serum had an APT reaction to the corresponding allergen. Furthermore, the positivity of APT was associated with allergen-specific lymphocyte proliferation and higher rates of CD69⁺, CD54⁺, and CD30⁺ after allergen stimulation *in vitro*.²¹

Fuiano and Incorvaia⁹ noted that the APT may also provide a positive result in patients with respiratory symptoms without current AEDS, and a European multicenter study⁸ reported that a substantial rate of patients with AEDS in clinical remission had exclusive positivity to APT. These observations led us to undertake the approach of dividing the patients according to current or past AEDS, using patients with rhinosinusitis and asthma without either current or past AEDS as a control group, and to compare the results of APT and SPT to mite extract. A positive APT result was observed in approximately 78% of patients, with no significant difference between current or past AEDS, and in 12% of control subjects. In contrast, positive SPT reactions to mites were found in 44.9% of control subjects compared with 7.7% of patients with current AEDS, 20.5% of those with current AEDS and respiratory disease, and 9.9% of those with past AEDS and current respiratory disease.

In this study, it is apparent that patients with AEDS have 2 different patterns of allergic response to allergens, one IgE mediated (as evaluated by positive SPT results) and the other cell mediated (as evaluated by positive APT results). The first kind of response became more frequent with the development of respiratory symptoms, along with increasing age, but decreased once AEDS was no longer clinically present. In contrast, the second kind of response persisted even after the disappearance of AEDS and was likely to be implicated in the pathogenesis of respiratory allergy when allergen specific IgE was not detected. Of course, this may be argued only for dust mites because we did not test other allergens. It is reasonable to suppose that in response to mites, sensitization through the skin, as already suggested, may lead to subsequent migration of sensitized T cells into the airways, causing respiratory disease.¹⁹

Furthermore, the role of IgE antibodies in such an immune response must not be overlooked because the increased ex-

pression of the high-affinity Fcε receptor 1 is considered important in facilitating the capture, processing, and presentation to T lymphocytes by skin dendritic cells. In an experimental model, the development of positive reactions to patch testing with aeroallergens required the presence of Fcε receptor 1+/IgE+ on Langerhans cells.¹⁷ On the other hand, it cannot be excluded that in individuals with negative SPT results, local production of specific IgE in the respiratory target organ is involved in the clinical symptoms.

In conclusion, the findings from this study should stimulate further research on the pathogenesis of AEDS, in particular addressing the possible differences in the kind of IgE production, and of inflammatory cells involved in the skin and respiratory tissues of patients with AEDS and rhinitis or asthma.

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REFERENCES

1. Ring J, Kunz B, Bieber T, Vieluf D, Przybilla B. The "atopy patch test" with aeroallergens in atopic eczema. *J Allergy Clin Immunol*. 1989;82:195.
2. van Voorst Vader PC, Lier JG, Woest TE, Coenraads PJ, Nater JP. Patch test with house dust mite antigens in atopic dermatitis patients: methodological methods. *Acta Dermatol Venereol*. 1991;71:301-305.
3. Darsow U, Vieluf D, Ring J. Atopy patch test with different vehicles and allergen concentrations: an approach to standardization. *J Allergy Clin Immunol*. 1995;95:677-684.
4. Darsow U, Vieluf D, Ring J; Atopy Patch Test Study Group. Evaluating the relevance of aeroallergen sensitization in atopic eczema with the atopy patch test: a randomized, double-blind multicenter study. *J Am Acad Dermatol*. 1999;40:187-193.
5. Nedorost ST, Cooper KD. The role of patch testing for chemical and protein allergens in atopic dermatitis. *Curr Allergy Asthma Rep*. 2001;1:323-328.
6. Shah D, Hales J, Cooper D, Camp R. Recognition of pathogenically relevant house dust mite hypersensitivity in adults with atopic dermatitis: a new approach? *J Allergy Clin Immunol*. 2002;109:1012-1018.
7. Giusti F, Seidenari S. Reproducibility of atopy patch tests with *Dermatophagoides*: a study on 85 patients with atopic dermatitis. *Contact Dermatitis*. 2004;50:18-21.
8. Darsow U, Laifaoui J, Kerschenlohr K, et al. The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. *Allergy*. 2004;59:1318-1323.
9. Fuiano N, Incorvaia C. Comparison of skin prick test and atopy patch test with dust mite extracts in patients with respiratory symptoms or atopic eczema dermatitis syndrome. *Allergy*. 2003;58:828.
10. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermatoven (Stock)*. 1980;92:44-47.
11. Fokkens W, Lund V, Bachert C, et al. EAACI position paper on rhinosinusitis and nasal polyps executive summary. *Allergy*. 2005;60:583-601.
12. Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology. Skin tests used in type I allergy testing Position paper. *Allergy*. 1989;44(suppl 10):1-59.
13. Kanof NB. The American Academy of Dermatology patch test series for contact dermatitis. *Int J Dermatol*. 1977;16:827-829.
14. Leung DYM. Atopic dermatitis: the skin as a window into the pathogenesis of chronic allergic diseases. *J Allergy Clin Immunol*. 1995;96:302-318.

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15. Leung DY, Bieber T. Atopic dermatitis. *Lancet*. 2003;361:151–160.
 16. Novak N, Bieber T, Leung DYM. Immune mechanisms leading to atopic dermatitis. *J Allergy Clin Immunol*. 2003;112:S128–S139.
 17. Leung DYM, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest*. 2004;113:651–657.
 18. Boguniewicz M, Leung DYM. Atopic dermatitis. *J Allergy Clin Immunol*. 2006;117:S475–S480.
 19. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol*. 2003;112:S128–S139.
 20. Spergel JM, Mizoguchi E, Oettgen H, Bhan AK, Geha R. Epicutaneous sensitization with protein antigens induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigens in mice. *J Clin Invest*. 1998;101:1614–1622.
 21. Wistokat-Wulfing A, Schmidt P, Darsow U, Ring J, Kapp A, Werfel T. Atopy patch test reactions are associated with T lymphocyte-mediated allergen-specific immune response in atopic dermatitis. *Clin Exp Allergy*. 1999;29:513–521.
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