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Diagnostic Performance of the Atopy Patch Test With Inhalant Allergens

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Abstract

Background: This study evaluated the diagnostic performance of the atopy patch test (APT) compared with skin prick testing (SPT) and in vitro IgE measurement in a large group of patients with atopic dermatitis (AD) with or without respiratory symptoms (RS).
Methods: The study included 521 patients (292 males, 229 females; age, 0.5-18 years; median age, 6 years) with AD and RS with different clinical presentations: current AD, 47 patients (Group A); current AD and RS, 72 patients (Group B), past AD and RS, 69 patients (Group C); and RS only, 280 patients (Group D). Fifty-three healthy individuals served as controls. All participants underwent the APT, SPT, and CAP/RAST with the most common inhalant allergens. The presence of a control group allowed calculation of specificity and positive and negative predictive values.
Results: A significant difference was found for a positive APT versus both SPT and CAP/RAST (P<.0001) but not for SPT versus CAP/RAST. The differences for APT were significant in all group comparisons except group B vs C and group C vs D. In the control group, the APT was positive in 2% of cases (specificity of 96.2%), SPT was positive in 6% of cases (specificity of 88.4%), and CAP/RAST was positive in 4% of cases (specificity of 92.5%).
Conclusions: In young patients sensitized to inhalant allergens with AD in addition to RS, the APT has a superior diagnostic performance to SPT and in vitro IgE measurement.

Key words: Atopy patch test. Skin prick test. In vitro IgE test. Diagnostic performance. Specificity.

Resumen

Antecedentes: En este estudio se ha evaluado la capacidad diagnóstica de las pruebas epicutáneas con alérgenos inhalantes comparadas con las pruebas cutáneas en "prick" y con la determinación de IgE específica, en una población pediátrica numerosa de pacientes sensibilizados a inhalantes con dermatitis atópica con o sin síntomas respiratorios asociados.
Métodos: En el estudio se incluyeron un total de 521 pacientes (292 varones, 229 mujeres, rango de edad 0,5 a 18 años, mediana 6 años) que presentaban los siguientes cuadros clínicos: dermatitis atópica activa, 47 pacientes (grupo A), dermatitis atópica y síntomas respiratorios activos, 72 pacientes (grupo B), antecedentes de dermatitis atópica y síntomas respiratorio no activos en la actualidad, 69 pacientes (grupo C) y solo síntomas respiratorios activos, 280 pacientes (grupo D); también se incluyeron como controles 53 sujetos sanos. A todos ellos se les realizaron pruebas epicutáneas con inhalantes, pruebas cutáneas en prick y determinación de IgE específica mediante técnica de CAST/RAST con una batería de inhalantes habituales de la zona. Se determinaron la especificidad y los valores predictivos positivos y negativos de la prueba.
Resultados: Encontramos diferencia significativas en el rendimiento diagnóstico entre las pruebas epicutáneas con inhalantes tanto frente a las pruebas cutáneas en prick, como frente a la determinación de IgE específica (p< 0,001). No encontramos, por el contrario, diferencias entre las pruebas cutáneas en prick y la determinación de IgE específica. Cuando comparamos los grupos, en el caso de las pruebas epicutáneas con inhalantes todas las diferencias fueron significativas excepto las comparaciones entre el grupo B frente al grupo C y el grupo C frente al grupo D. Las pruebas epicutáneas con inhalantes fueron positivas en el 2% de los controles sanos, las pruebas cutáneas en prick en el 6% y la determinación de IgE específica en el 4%, lo que corresponde a una especificidad del 96,2% para las pruebas epicutáneas, del 88,4% para las pruebas en prick y del 92,5% para la determinación de IgE específica.
Conclusiones: En pacientes pediátricos sensibilizados a inhalantes, no solo con dermatitis atópica sino también con síntomas respiratorios, las pruebas epicutáneas tienen una capacidad diagnóstica superior a las pruebas en prick o la determinación de IgE específica.

Palabras clave: Pruebas epicutáneas con inhalantes. Pruebas cutáneas en prick. Capacidad diagnóstica. Especificidad.

Introduction

The atopy patch test (APT) was introduced in 1989 as a diagnostic tool to demonstrate the involvement of a T-cell mediated mechanism in patients with atopic dermatitis (AD) [1]. Recent research has provided evidence that allergic symptoms in patients with respiratory diseases such as rhinitis and asthma may also be sustained by T cell–mediated reactions as assessed by a positive APT result and frequently negative results in common diagnostic tests, such as skin prick testing (SPT) and in vitro tests to detect allergen-specific IgE antibodies [2-5]. Clinical data on the role of the APT are supported by robust laboratory evidence on the capacity of this test to reproduce the pathophysiologic events of AD. First, in biopsy-based studies, a T_H2 cytokine pattern has been found 24 hours after the APT, with a shift to a T_H1 pattern, as occurs in chronic AD skin lesions, after 48 hours [6-7]. Second, an influx of inflammatory dendritic epidermal cells has been observed after application of the APT to the skin of AD patients [8]. Third, compared with patients without lymphocyte proliferation, patients with allergen-specific lymphocyte proliferation and expression of activation markers on peripheral blood T cells following in vitro stimulation with house dust mite (HDM) extracts as well as cat and grass pollen extracts have a higher proportion of positive APT results [2]. Fourth, immunohistochemical studies have demonstrated the presence of IgE on Langerhans cells in positive APT reactions to HDM in patients with mite-induced AD [9].

We compared APT, SPT, and in vitro IgE measurement results in a large group of patients with AD, with or without rhinitis or asthma. Tests were also performed in a control group of healthy individuals to assess specificity and positive and negative predictive values.

Patients and Methods

Patients

The study was performed in the pediatric allergy service in Torremaggiore in Foggia, Italy using a population of 521 individuals aged between 0.5 and 18 years (mean age, 6 years). There were 292 males (56%) and 229 females (44%). All the patients had been referred to the service by their pediatrician or family doctor because of AD and/or respiratory symptoms, and were consecutively included in the study. The patients were allocated to 4 different groups according to their clinical history. Group A included patients with current AD, Group B included patients with current AD and respiratory symptoms, Group C included patients with past AD and respiratory symptoms, and Group D included patients with respiratory symptoms only. Patients with a family or personal history of allergic reactions to foods or positive SPTs to food extracts were excluded to rule out an influence of food allergy on AD or respiratory symptoms.

Fifty-three healthy controls (27 males, 50.9%; 26 females, 49.1%) aged between 0.9 and 13.6 years (mean age, 6.7 years) were included, following informed consent from their parents. The inclusion criteria for the control group were a negative family and personal history of atopy and absence of any symptoms or signs possibly related to atopic diseases at 3 medical evaluations held at 1-month intervals.

Methods

AD was diagnosed according to the criteria of Hanifin and Rajka [10] and allergic rhinitis and asthma were diagnosed according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines [11]. All patients and their parents were informed that antihistamines and topical corticosteroids should be avoided for 1 week before testing. At the test visit, the patients underwent SPT with inhalant allergen extracts from Stallergénes. The SPT results were evaluated according to the guidelines from the European Academy of Allergy and Clinical Immunology, with the minimum positive result for a wheal diameter defined as 3 mm [12]. Only positive results consistent with the patients' clinical history were considered. At the same visit, the patients also underwent APT performed by the same operator (N.F.) using allergen extracts from Chemotechnique Diagnostics. Table 1 shows the list of allergens tested and their concentration. The vehicle used was white petrolatum, which was amalgamated with the allergens by heating at a temperature not exceeding 40°C. Each test substance was applied to intact skin on the lower back and held firmly in position for 48 hours using adhesive patches (aluminium Finn chambers with an inner diameter of 8 mm, an area of 50 mm^2, and a volume of about 20 μL). To correctly evaluate positive responses, a negative petrolatum control was used. The test results were read no less than 30 minutes after removal to avoid the margin effect. A further reading was done after 72 hours. Results were interpreted according to the recommendations of the American Academy of Dermatology for APT, with a scale ranging from + (weak reaction) to +++ (very strong reaction) [13]. Only reactions classified as ++ and +++ were considered positive for the purpose of the study. In vitro measurement of specific IgE was performed with the CAP/RAST technique using material from Phadia. A positive result was defined, as suggested by the manufacturer, as a level of specific IgE higher than 0.10 Ku/L. The allergens tested in the APT, SPT, and CAP/RAST were the most commonly occurring allergens in our geographical area and included grass pollen, cypress pollen, *Parietaria* pollen, Compositae pollen, HDM, *Alternaria tenuis*, and cat epithelium.

Table 1. Position of Tested Allergens as Given by the Manufacturer and Respective Concentrations

Position	Name	g ±10%
1	Alternaria	0.085
2	Cat epithelium	0.086
3	7 Grass	0.084
4	Dermatophagoides	0.085
5	Compositae Mix	0.086
6	Cypress	0.088
7	Parietaria	0.088
8	Petrolatum control	0.085

Table 2. Demographic and Baseline Characteristics of the Study Population

	Group A Current AD	Group B Current AD + RS	Group C Past AD + RS	Group D RS Only	Control Group
Total	47	72	69	280	53
Sex, No (%)					
M	20 (42.5%)	44 (61.1%)	39 (56.5%)	162 (58.0 %)	27 (50.9%)
F	27 (57.5%)	28 (38.9%)	30 (43.5%)	118 (42.0 %)	26 (49.1%)
Age, y					
Range	0.4 – 7.9	0.6 – 16.5	1.6 – 14.6	0.7 – 18.0	0.9 – 13.6
Mean (SD)	2.5 (1.8)	5.5 (3.4)	6.1 (3.0)	7.7 (4.0)	6.7 (3.0)
Median	1.9	4.9	5.5	7.2	8.0

Abbreviations: AD, atopic dermatitis; RS, respiratory symptoms (rhinitis, asthma).

Ethical approval was not needed for the patient group because we used common tests for the routine diagnosis of allergy.

Statistical Analysis

Data are presented as percentages and means (SD) for qualitative and quantitative variables, respectively. The statistical analysis was performed using the $\chi 2$ test for categorical variables and analysis of variance and Bonferroni multiple comparison tests for continuous variables. Contingency tables were used to analyze the association between categorical variables (sex and positive family history) and the tests used in the study (APT, SPT, and CAP/RAST) and to perform univariate analysis of APT, SPT, and CAP/RAST positivity in the 4 groups. Statistical significance was set at a *P* value of less than .05. All statistical analyses were performed using BMPD statistical software (version 2007). Positive and negative predictive values, with 95% CIs, were calculated as appropriate.

Results

The population of patients included 468 children and adolescents (265 males, 56.6%; 203 females, 43.4%) with a median age of 6 years and a mean (SD) age of 5.8 (3.9) years. The allocation to the 4 groups was as follows: Group A (current AD), 47 patients; Group B (current AD and respiratory symptoms), 72 patients; Group C (past AD and respiratory symptoms), 69 patients; and Group D (respiratory symptoms only), 280 patients. Table 2 reports the demographic characteristics of the 4 groups of patients and the control group. Regarding the clinical stage of AD according to the criteria of Hanifin and Rajka [10], disease was mild (SCORing Atopic Dermatitis [SCORAD], <20) in 54 (45.4%) of the 119 patients with current AD, moderate (SCORAD, 20-40) in 43 of the patients (36.1%), and severe (SCORAD, >40) in 22 (18.5%) of the patients. The negative control (petrolatum) was negative in all patients. In the control group of 53 individuals, there was 1 positive response to APT, 3 positive responses to SPT, and 2 positive responses to CAP/RAST. These numbers give a specificity of 98.2% for the APT, 94.3% for SPT, and 96.2% for CAP/RAST, respectively. The overall number of positive responses in the group of patients was 237 (50.6%) for the APT, 121 (25.8%) for SPT, and 133 (28.4%) for CAP/RAST. The difference was significant for a positive APT versus both SPT and CAP/RAST ($P<.0001$) but not for a positive SPT versus CAP/RAST ($P=.55$). The positive and negative predictive 95% CI values were 99.2-99.6 and 16.1-20.7 for the APT, 96.8-98.3 and 11.0-14.2 for SPT, and 97.9-99.1 and 11.5-14.9 for CAP/RAST. The specific values for each of the groups (A, B, C and D) are shown in Table 3. The APT was positive

Table 3. Positive and Negative Predictive Values for the APT, SPT and CAP/RAST[a]

	PPV	NPV
APT		
Group A	90.1-95.6	55.2-65.7
Group B	96.3-99.6	63.1-73.7
Group C	95.9-99.3	59.7-70.3
Group D	98.7-99.9	23.2-29.5
SPT		
Group A	44.8-55.1	48.0-58.3
Group B	80.6-87.7	42.3-52.0
Group C	81.4-88.5	44.1-54.0
Group D	95.4-97.7	17.8-23.0
CAP/RAST		
Group A	70.9-79.1	40.8-50.2
Group B	85.8-91.9	42.8-52.5
Group C	90.2-95.5	49.1-59.4
Group D	96.7-98.7	18.1-23.3

Abbreviations: APT, atopy patch test; NPV, negative predictive power; PPV, positive predictive power; SPT, skin prick test.
[a]Data shown as 95% CIs.

Table 4. Positive Test Results According to Median Age[a]

	≤6 y vs >6 y	X^2	*P* Value
APT	115 vs 122 (22.1 vs 23.4)	1.68	.19
SPT	22 vs 99 (4.2 vs 19)	70.6	<.001
RAST	53 vs 80 (10.2 vs 15. 4)	9.93	.002

Abbreviation: APT, atopy patch test.
[a]Positive results shown as number (%) of patients.

Table 5. Positive Test Results in the 4 Groups of Patients and Controls According to Age

	≤6 y vs >6 y (No. of Patients)	≤6 y vs >6 y (% of Patients)	X^2	*P* Value
APT groups				
Controls	1/21 vs 0/32	(4.8 vs 0)	1.55	.212
A: Current AD	12/45 vs 1/2	(26.7 vs 50)	0.521	.47
B: Current AD with RS	26/45 vs 22/27	(58.7 vs 81.5)	4.267	.038
C: Past AD with RS	24/42 vs 17/27	(57.1 vs 63)	0.231	.63
D: RS only	53/116 vs 82/164	(45.7 vs 50)	0.506	.476
OR = 0.8079 95% CI = 0.572 – 1.1411 X^2 = 1.467 *P* value = 0.225				
SPT groups				
Controls	0/21 vs 3/32	(0 vs 9.4)	2.077	.148
A: Current AD	3/45 vs 0/2	(6.7 vs 0)	0.142	.706
B: Current AD with RS	7/45 vs 9/27	(15.6 vs 33.3)	3.086	.078
C: Past AD with RS	2/42 vs 15/27	(4.8 vs 55.6)	22.836	<.001
D: RS only	10/116 vs 75/164	(8.6 vs 45.7)	44.26	<.001
OR = 0.131 95% CI = 0.0792 – 0.2167 X^2 = 74.838 *P* value < 0.001				
RAST groups				
Controls	0/21 vs 2/32	(0 vs 6.2)	1.364	.242
A: Current AD	5/45 vs 1/2	(11.1 vs 2.1)	2.6	.106
B: Current AD with RS	8/45 vs 8/27	(17.8 vs 22.2)	1.371	.246
C: Past AD with RS	14/42 vs 12/27	(33.3 vs 44.4)	0.864	.352
D: RS only	26/116 vs 59/164	(22.4 vs 35.9)	5.911	.015

Abbreviations: AD, atopic dermatitis; APT, atopy patch test; RS, respiratory symptoms (rhinitis, asthma), SPT, skin prick test.

in 22 (40.7%) of 54 patients with mild AD, 25 (58.1%) of 43 patients with moderate AD, and 14 (63.6%) of 22 patients with severe AD; these differences were not significant. Table 4 shows the positive test results for patients aged 6 years and under versus older patients; a significantly higher rate of positive SPT and RAST was observed in patients aged over 6 years. Table 5 shows the test results for the different groups of patients and controls using the same age cutoff. For the APT, all the differences were significant except for Group B versus C and Group C versus D, where no age-related differences were observed. In the case of SPT and RAST, the rate of positive tests was significantly higher in children aged more than 6 years. Table 6 shows the results for the tests with the different allergens used in the study and highlights the prominent role of HDM.

Discussion

Although introduced in the late 1980s [1], the ATP has played a limited role in the diagnosis of allergy until recently, when a number of studies called attention to its capacity to detect allergy in patients with AD in addition to rhinitis or asthma with negative SPT and in vitro IgE results [14]. This is of particular interest, because AD patients with negative SPT and specific IgE results in serum should be classified as nonatopic in the absence of an APT. In a European multicenter study of 314 patients with AD, the frequency of positive APT reactions to HDM was 39%, and a positive APT without SPT or specific IgE for the respective allergen was seen in 17% of patients [15]. Additional observations have also highlighted the value of the APT. In one study, exclusive APT positivity for HDM was observed in children with respiratory symptoms [3] and in another, 25% of children with mite-induced asthma and rhinitis with positive SPT and specific IgE in serum had a positive APT to HDM, indicating that delayed hypersensitivity is concurrent with immediate hypersensitivity [6]. Further studies have investigated the factors underlying positive APT results in individuals with respiratory symptoms. One study of 297 children showed that a positive APT to HDM in individuals with asthma or rhinitis was strongly associated with the presence of current or past AD and that most individuals with respiratory disease and a negative history for AD had a positive SPT [5]. In the same study, multivariate analysis showed that the odds of a positive APT result was greatly increased in patients with AD (OR, 17.4), patients with AD and respiratory disease (OR, 21.9), and patients with past AD and respiratory disease (OR, 22.8). These observations were confirmed in a subsequent study of 465 children, divided into 4 groups: current AD, current AD with respiratory symptoms, past AD with respiratory symptoms, and respiratory symptoms with no history of AD [16]. The APT was significantly more frequently positive in groups with current or past AD than in the group with respiratory symptoms only. SPT and specific IgE in serum, in turn, were significantly more frequently positive in the group with respiratory symptoms only. These significant differences in APT responses in patients with dissimilar clinical expressions suggest that distinctive immunologic mechanisms underlie the different manifestations of hypersensitivity to HDM. It is conceivable that sensitization to mites in individuals with a negative history of AD occurs through the respiratory route, leading to the development of a T_H2 response pattern with ongoing production of specific IgE and consequent positive SPT and in vitro IgE tests. By

Table 6. Percentage of Positive Test Results by Allergens

	Control Group			Group A Current AD			Group B Current AD + RS			Group C Past AD + RS			Group D RS Only		
	SPT	APT	RAST	SPT	APT	RAST	SPT	APT	RAST	SPT	APT	RAST	SPT	APT	RAST
Alternaria								2.8%		4.3%	1.4%	7.2%	5.4%	2.1%	4.3%
Cat epithelium			1.9%				2.8%	1.4%	4.2%			10.1%	3.2%	0.7%	5.0%
Grass pollen	1.9%				2.1%	2.1%	4.2%	4.2%	8.3%	7.2%	2.9%	5.8%	14.3%	3.9%	11.4%
Dust mite	1.9%	1.9%		6.4%	23.4%	6.4%	15.3%	63.9%	16.7%	15.9%	55.1%	27.5%	16.1%	42.5%	14.6%
Compositae pollen			1.9%				2.8%	2.8%				2.9%	0.7%	0.4%	3.6%
Cupressaceae pollen	1.9%				2.1%	4.3%			5.6%		1.4%	4.3%		0.4%	6.4%
Parietaria pollen					2.1%	2.1%			4.2%	2.9%	2.9%	8.7%	2.1%	1.8%	6.1%
Total	5.7%	1.9%	3.8%	6.4%	29.7%	14.9%	25.1%	75.1%	39.0%	30.3%	63.7%	66.5%	41.8%	51.8%	51.4%

Abbreviations: AD, atopic dermatitis; APT, atopy patch test; RS, respiratory symptoms (rhinitis, asthma), SPT, skin prick test.

contrast, if the mite allergens enter through the skin, as occurs in exposure to common indoor concentrations of the major allergen Der p 1 [17] (this entry being facilitated by the proteolytic activity of HDM and the presence of a skin barrier dysfunction), a different sequence of events is likely to take place, which is reflected by the positive APT and negative SPT and in vitro IgE tests. In the present study we evaluated response to APT, SPT and in vitro IgE tests to common environmental allergens in a large population of atopic children divided into subgroups based on a positive or negative history for AD and the presence or absence of respiratory symptoms as well as age-related subgroups, using the median age of 6 years as a cutoff. By including a healthy control group, we were able to calculate, for what we believe is the first time, specificity and positive and negative predictive values for the APT. Very good values were obtained for both specificity and positive predictive value; they were higher than 90% in all cases and better than SPT and RAST in all study groups. The negative predictive value, however, was unsatisfactory (<60% in all cases), although it was higher for APT. Nonetheless, the overall data from this study add strength to the high value of the APT, particularly in patients with a history of current or past AD, and also highlights the important role of HDM, which is currently the major cause of AD in children [18]. The APT showed a high rate of positive results in all study groups, while SPT and in vitro IgE tests were mostly positive in children aged over 6 years. This suggests that a positive response to IgE tests becomes more common with age, indicating that IgE determination may be the most appropriate test for adults, in whom the IgE-mediated mechanism prevails. In the case of children, however, and especially those with a history of AD, the cell-mediated mechanism would appear to be more important than commonly thought. Thus, there may be 2 different models of natural history of sensitization to inhalant allergens: one with a persistent cell-mediated mechanism and another in which this mechanism is replaced over time by the IgE-mediated mechanism. This theory would be valid for children and adolescents, but no studies are currently available for adults. A greater understanding of the issue could change the attitude of allergy specialists regarding the use of the ATP, particularly when evaluating patients with rhinitis or asthma who have a past history of AD and a negative IgE test.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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