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Phadiatop® in the diagnosis of respiratory allergy in children: Allergy Project – PROAL

Charles K. Naspitz[1], Dirceu Solé[1], Maria Cecília Aguiar[4], Maria Letícia Chavarria[2], Nelson Rosário Filho[1], Antônio Zuliani[2], Eliana C. Toledo[3], Bruno A. P. Barreto[3], Leda S. F. Souza[2], Grupo PROAL

Abstract

Objectives: To evaluate the positivity of Phadiatop® in children from several Brazilian pediatric allergology centers and to compare its results with the presence of serum specific IgE to inhalant and food allergens.

Patients and method: Phadiatop® and serum specific IgE levels (RAST) to inhalant and food allergens (UniCAP® - Pharmacia) were measured in 457 children from several pediatric allergy centers and in a non-allergic control group (n = 62), distributed across five age groups.

Results: Phadiatop was positive in 305 atopic children (67.6%) and in 25.8% of controls ($p < 0.001$). Among atopic children the distribution of positive test varied according to age: 7.9% (24/305) among under 2 year-olds, 15.4% (47/305) in 2 to 3 year-olds, 22% (67/305) in 3 to 4 year-olds, 19.3% (59/305) in 4 to 5 year-olds and 35.4% (108/305) in 5 to 12 year-olds. No concordance between food allergens and Phadiatop® was observed. Analysis of the relationship between positive inhaled allergen RASTs and positive Phadiatop® showed best indices with house dust mites (*D. pteronyssinus, D. farinae* and *Blomia tropicalis*).

Conclusions: Phadiatop® is a useful tool for diagnosing domestic mite allergy.

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Introduction

Recent studies have documented an increase in the prevalence of allergic diseases in several different parts of the world. In Brazil the prevalence of medical diagnosis of asthma, allergic rhinitis and atopic eczema were recorded for the first time as part of an international study and were found to be, on average, 21%, 39% and 8% respectively.[1-3] The presence of IgE antibodies specific to usual antigens that characterizes allergic diseases is an important parameter on which diagnosis confirmation can be based.[4]

When assessing an allergic individual, clinical history plays a fundamental role. It allows causative and aggravating factors to be verified, which is important for the future establishment of treatment plans, in addition to the providing information on the natural history of the disease. Recent studies, however, have pointed to false positive rates of up to 22.6% when clinical history is used in isolation to diagnose allergic disease.[5-7]

As a result of this, many professionals have come to value confirmatory laboratory tests for establishing more precise diagnoses of allergic diseases. In general these tests entail additional costs to the patient. Thus the employment of a test that was capable of identifying multiple sensitizations would be a strong argument for its application in a more generalized manner.

1. Full professor, Brazilian Society of Pediatrics – Department of Allergy and Immunology.
2. Associate professor, Brazilian Society of Pediatrics – Department of Allergy and Immunology.
3. Assistant professor, Brazilian Society of Pediatrics – Department of Allergy and Immunology.
4. Specialist in Allergology and Immunopathology, Brazilian Society of Pediatrics – Department of Allergy and Immunology.

PROAL Group - Cristina Abe Jacob, Emanuel C. S. Sarinho, Francisco J. P. Soares, Luiza Karla de Paula Arruda, Márcia C. Mallozi, Maria Marluce Santos Vilela, Neusa F. Wandalsen, Paulo Silva da Silva, Thales Barba, Vera Dantas, Wellington Borges, Wilson Rocha Filho, Judith Arruda.

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In the diagnosis of respiratory allergy Phadiatop® has become one of the most widely used *in vitro* tests. Phadiatop® is a simple test that is capable of detecting the presence of IgE specific to the inhalant allergens that are most common in the tested environment simultaneously.[8] Nevertheless, it must have the allergens with the greatest prevalence of sensitization, among atopic individuals, in the environment it is being used in.[8]

In Brazil, despite its use as a diagnostic screening test for respiratory allergies, the real correlation between Phadiatop® and positivity to the inhalant allergens most common among the Brazilian allergic population is unknown. This being the case, the objectives of this study were to evaluate the frequency of Phadiatop® in children from different locations in Brazil treated at pediatric allergology centers and to compare it with sensitization to inhalant and food allergens as evaluated by specific IgE assay in serum, in the same locations.

Patients and methods

This was a case-controlled study in which 457 children (177 girls [38.7%] and 280 boys [61.3%]) participated. They were aged between 12 and 144 months, cared for at allergology services located in all five regions of the country. The children were split into five age groups as follows: younger than 2 years, 2 to 3 years, 3 to 4 years, 4 to 5 years and 5 to 12 years. Children were classed as atopic if they exhibited at least one positive immediate hypersensitivity skin test (average wheal diameter greater than or equal to 3 mm) to at least one inhalant or food allergen, tested and selected randomly. The control group was made up of 62 other children originating from investigative centers of the Northeast, Southeast and South regions who had needed blood tests for other reasons, such as preoperative assessment for elective surgery. All controls had a history free of allergic disease and negative immediate hypersensitivity skin test for the allergens employed at the respective centers.[9]

Depending on the reason for referral, patients were classed as: wheezing infants (n = 20), food allergy (n = 16), atopic dermatitis (n = 56), and respiratory allergy (n = 348). Babies were defined as wheezing if they were less than two years old and presented recurrent episodes of wheezing and other possible causes had been ruled out (aspiration syndromes, fibrocystic disease, airway malformations among others). Patients with proven asthma and/or rhinitis were defined as having respiratory allergies.

Peripheral blood samples were taken from both allergic and control patients so that IgE serum levels specific to inhalant allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*, cat, dog, fungus, cow's epithelium, horse, grasses and cockroach) and food allergens (cow's milk, egg, peanut, wheat and seafood panel) could be assayed and inhalant allergens tested with Phadiatop® (UniCAP®-Pharmacia).[12,13] Phadiatop® is a selective test composed mainly of a mixture of domestic dust and mites: *Dermatophagooides pteronyssinus* and *D. farinae* and as such its result is qualitative (present or not). Specific IgE levels (RAST) greater than or equal to 0.35 UI/ml (class 1) were defined as positive.[10,12] The study was approved by the relevant Ethics Committees and informed consent forms were signed.

Non-parametric tests were employed to analyze variables and coefficients for sensitivity, and specificity, positive and negative predictive values and agreement were calculated.[13] In all cases the cut off for null hypothesis rejection was set at 5%.

Results

Divided by sex, the group of allergic children contained 38.6% (174/451) girls and 61.4% (277/451) boys. Comparable figures were observed in the non-allergic controls: 41.9% (26/62) girls and 58.1% (36/62) boys. Distribution by age group is shown in Table 1.

Table 1 - Distribution of Phadiatop® positive children by age group

Age group (years)	Allergic			Controls		
	Total	n	%	Total	n	%
< 2 (a)	79	24	30.8	12	2	16.7
2-3 (b)	83	47	56.6	13	3	23.1
3-4 (c)	102	67	65.7	9	3	33.3
4-5 (d)	81	59	72.8	13	4	30.7
5-12 (e)	112	108	96.4	15	4	26.7
Total	457	305	67.6	62	16	25.8

Chi-square: allergic children > controls. Chi-square test.
Allergic significant value: a < b, c, d, e; b, c < d, e; c, d <e; d < e.

Table 2 shows the distribution of allergic patients by age group and region of origin. Taking each of the regions individually there were no significant differences in distribution for each age group. The same was true of sex (data not shown) and when the entire sample was analyzed together. Table 1 shows the distribution of Phadiatop® positive children. Phadiatop® positivity was significantly greater among the allergic subjects. There was no difference in Phadiatop® positivity related to sex in the allergic group (64.9% of the girls and 69.4% of the boys) or in the control group (62.5% for boys and girls). In the allergic group, frequency increased significantly with age. In Table 3 the results of positive and negative agreement between the RAST and Phadiatop® tests can be observed. Statistical analysis showed that only comparisons between Phadiatop® and domestic dust mites were significant. There was no significant agreement with the remaining allergens. Table 4 lists the calculated indices for sensitivity, specificity, positive and negative predictive values and for agreement between Phadiatop® and RAST for domestic dust mites. In Table 5

Table 2 - Distribution of allergic patients by age group and region of origin

Age group (years)	Total		N/NE*		CW*		SE*		S*	
	n	%	n	%	n	%	n	%	n	%
< 2	79	17.3	18	13.9	12	23.1	38	16.9	11	21.6
2-3	83	18.2	25	19.3	10	19.2	40	17.8	8	15.7
3-4	102	22.3	27	20.9	13	25.0	53	23.6	9	17.6
4-5	81	17.7	30	23.4	9	17.3	33	14.7	9	17.6
5-12	112	24.5	29	22.5	8	15.4	61	27.0	14	27.5
Total	457	100.0	129	100.0	52	100.0	225	100.0	51	100.0

Chi-square test: no differences between age groups in each region and total.
*N/NE = north and northeast; CW = central west; SE = southeast; S = south.

rates of RAST for domestic mites and Phadiatop® positivity are shown by primary complaint. We observed the lowest values among the wheezing babies and patients with food allergies. In contrast, among patients with atopic dermatitis sensitization to domestic mites was as elevated as among those with respiratory allergies.

Discussion

The clinical manifestations of allergic diseases are often the same as with other diseases which makes their diagnosis difficult. Therefore, clinical practitioners often feel the need for a laboratory test that is capable of identifying them in a suitable manner. If the test combines low costs, speed of execution, availability at most laboratories and a high level of sensitivity in identifying its target population, then we have a good instrument to be used in epidemiological studies of allergic disease prevalence. Phadiatop® has been widely used as a screening test for respiratory allergies.[5,14,15]

In principal Phadiatop® is an *in vitro* test that allows individuals who are sensitive to multiple inhalant allergens to be identified simultaneously. In order to be a useful and sensitive method Phadiatop® must be constituted of the aeroallergens that are most prevalent in the area of study. In Brazil, a number of different studies of selected allergic populations have also shown elevated prevalence of sensitization to the domestic dust mites: *D. pteronyssinus, D. farinae* and *Blomia tropicalis* and, less often: animal epithelia, cockroach allergens and, more seldom, fungi.[16-18]

Depending on the population being studied, the rate of Phadiatop® positivity can vary. It will be lower among younger children or normal subjects and higher among patients with respiratory allergies.[19,20] Smith-Sivertsen et al. performed a comparative study of the prevalence of allergic respiratory disease in two adult populations living in two different countries, Russia and Norway, but living in adjacent regions.[21] In addition to a specific questionnaire about symptoms, Phadiatop® was used as a screening test to identify sensitized individuals.[21] The authors reported that 20.7% of the Norwegians and 25.7% of the Russians were Phadiatop® positive. Tschopp et al. observed Phadiatop® positivity in 29% of the normal adults they assessed.[19] On the other hand, Williams et al. observed a rate of 71.7% positivity among patients with a clinical diagnosis of respiratory allergy.[5]

In the current study we found that 67.6% of the children with allergic diseases and 25.8% of those without allergies were positive when tested with Phadiatop®. The apparently

Table 3 - Results of positive and negative agreement between the RAST and Phadiatop® tests

Allergen	Agreement		
	positive	negative	geral (%)
D. pteronyssinus	288	133	93.3*
D. farinae	286	141	94.7*
Blomia tropicalis	239	136	83.2*
Cockroach	146	144	64.3
Cat	53	145	43.9
Grasses	45	146	42.2
Cow's epithelium	34	135	37.5
Dog	33	144	39.2
Horse	19	146	36.6
Fungus	12	145	34.8
Fish	129	142	60.1
Egg	89	125	47.5
Wheat	79	135	47.5
Cow's milk	78	120	43.9
Peanut	59	142	44.6
Soya	50	143	42.8
Corn	44	142	41.2

Kappa test* $p < 0.05$.

Table 4 - Indices for sensitivity (SS), specificity (S), positive and negative predictive values (PPV, NPV) and for agreement (A) between Phadiatop® and RAST for domestic dust mites

RAST positive	SS (%)	S (%)	PPV (%)	NPV (%)	A (%)
D. pteronyssinus	94.3	91.5	96.1	87.8	93.3
D. farinae	94.6	96.4	98.4	88.9	94.7
Blomia tropicalis	79.4	92.9	96.2	66.8	64.3

Table 5 - Distribution of patients (%) according to primary complaint and positivity for domestic mites and Phadiatop®

Test	Wheezing babies (n = 20)	Food allergy (n = 16)	Atopic dermatitis (n = 66)	Respiratory allergy (n = 348)
D. pteronyssinus	40.0	62.5	80.4	76.7
D. farinae	35.0	43.8	78.6	73.6
Blomia tropicalis	20.0	18.8	64.3	69.8
Phadiatop®	40.0	56.3	82.1	77.3

reduced rate of positivity to Phadiatop® among allergic children is the result of the fact that we included patients with non-respiratory manifestations in the calculation. There was a 40% positivity level among the wheezing babies and those with food allergies were 56% positive. These results are explained by young patients and type of allergic disease respectively.[22,23] Nevertheless, positivity to Phadiatop® was elevated among atopic dermatitis patients, i.e. 82.1%. There is controversy over the role played by mites as aggravating or causative agents of atopic dermatitis. Additionally, it is known that around 50% of these patients will progress to allergic respiratory disease.[22,23] Patients with atopic dermatitis and serum IgE specific to domestic dust mites exhibit improvements when their environmental exposure to domestic dust mites is controlled.[24,25] The rate of positivity among patients with respiratory allergies was 77.3%, which is comparable to those observed by others.[5,15,21]

Another use of a allergy diagnostic test would be its use as a predictive method for later allergic disease development. A number of different researchers studied the positivity of Phadiatop® as a marker for allergic disease, in particular respiratory ones. Lilja et al. in a follow-up study from birth to five years of age, of children at risk of developing asthma, children of asthmatics parents, were tested with Phadiatop® at six months, at 18 months and at five years.[14] Of the children whose exams were positive at six months, 75% had manifested as asthmatic at 18 months and all of them had done so by five years of age.[14] This being the case, the authors found that Phadiatop® had a predictive value of 80% for predicting asthma in at-risk infants. This value is significantly superior than the 53% that would be the case if a positive aeroallergen skin test result had been included in the diagnostic criteria.[14]

Kotaniemi-Syrjanen et al. studied Phadiatop® as a predictive test for the development of asthma in infants less than two years old that had been hospitalized for acute wheezing. Blood samples were taken at this point and stored until the children were at least five years old.[15] They were then followed until school age at which point they were assessed for asthma and/or other allergic manifestations and levels of serum IgE specific to inhalant and food allergens were assayed. Forty percent of the initial population progressed to asthma and Phadiatop® was positive in 18% of the entire group and all of these patients became asthmatic.[15] In an attempt to identify risk factors for hospital admission and readmission because of acute exacerbations in children under four years old with asthma, Wever-Hess et al. recorded that sensitization to aeroallergens (positive Phadiatop® test) was associated with an eight times greater risk of recurring exacerbations.[26]

Doubt remains as to which of the many different screening methods routinely employed is the most appropriate: anamnesis, immediate hypersensitivity skin tests, specific

IgE serum assay or Phadiatop®. Williams et al. studied the value of Phadiatop® as a diagnostic method for sensitization in allergic children and adolescents, treated at specialist services.[5] Results were compared with those from immediate hypersensitivity skin tests for aeroallergens, with specific IgE and with clinical history. According to Williams et al. clinical history induced a false positive result in around 23% of cases. The laboratory tests had a good correlation. Phadiatop® was positive in 73.1% of those who had positive skin tests, in 71% of those with positive RAST and in 71.7% of all patients. There was 99% agreement between Phadiatop® positive patients with specific IgE serum tests and 98% agreement with positive immediate hypersensitivity skin tests and 83.2% with positive clinical history. Agreement levels were also elevated among those with negative Phadiatop® tests.[5]

Tschopp et al. studied the diagnostic value of immediate hypersensitivity skin test, total IgE serum levels and Phadiatop® in a Swiss adult population.[26] The prevalence of allergic asthma was 1.8% and that of allergic rhinitis was 16.3%. In the overall population the prevalence of positive Phadiatop® results was 29%, and positivity was 23% for both the skin tests and total IgE serum assays. The sensitivity of Phadiatop® for the diagnosis of allergic asthma was significantly higher than that of the skin tests (72.5% vs. 65.4%) and the same was true of allergic rhinitis (77.1% vs. 68.4%); both were better than IgE serum levels. Nevertheless, specificity and efficiency were better for the skin tests than for Phadiatop®.[27]

While it was already known that Phadiatop® is constituted from inhalant allergens, no studies had been performed in our country that identified these allergens. This being the case, a comparative study of Phadiatop® positivity and the various tests for serum IgE specific for several different allergens was performed. With the intention of confirming that food allergens were not included in Phadiatop® we included children with food allergies in the research. The highest levels of agreement were found with the domestic dust mites: *D. pteronyssinus, D farinae* and *Blomia tropiclais.* Using Phadiatop® as a method for diagnosing sensitization to each of the mites we were able to establish its sensitivity, specificity and positive and negative predictive values (Table 4).

In conclusion, we have proved in this study that Phadiatop® positivity is elevated among children with respiratory allergy, and that domestic dust mites are the main constituents. The high levels of agreement, sensitivity, specificity and positive and negative predictive values indicate that Phadiatop® is a useful test for identifying patients sensitized to domestic dust mites.

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Corresponding author:
Dirceu Solé
Rua Mirassol, 236/72
CEP 04044-010 - São Paulo, SP, Brazil
Tel.: +55 (11) 5579.3778
E-mail: dirceus@nox.net; dirceus@ajato.com.br