

Use of Phadiatop[®] Infant in diagnosis of specific sensitization in young children with wheeze or eczema

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Wheezing and eczema are common symptoms in young children and it is important to disclose sensitization for correct management. The objective of this study was to assess the diagnostic values of Phadiatop Infant, an *in vitro* test for graded determination of immunoglobulin E (IgE) antibodies to food and inhalant allergens. One-hundred and forty-nine children (median age 1.4 yr) with symptoms of wheezing (51%) eczema (28%) or a combination of both (21%) were classified as atopic or non-atopic based on case history, atopic history, physical examination and determination of IgE antibodies. The clinical performance of Phadiatop Infant was evaluated for 145 children against this classification in a blinded manner to the allergist. Fifty-one children were classified as atopic of which Phadiatop Infant identified 49. Ninety-four were non-atopic of which the test identified 90. This resulted in a sensitivity of 96%, a specificity of 96%, a positive and a negative predictive value of 94% and 98%, respectively. Logistic regression showed that probability had to be assessed as atopic increased with increasing Phadiatop Infant values. These results suggest that Phadiatop Infant can be recommended as an adjunct to the clinical information in the differential diagnosis on IgE-mediated allergy in young children. The test thus provides an opportunity for early correct diagnosis and identification of subjects at risk for whom intervention may be necessary.

Wheezing and eczema are common symptoms in young children. Airway symptoms can have an atopic background but also be due to other underlying causes, such as bacterial or viral infections (1–5). Therefore, it is not always easy to make a correct diagnosis only by case history and physical examination. The atopic march often begins with food allergy and atopic dermatitis followed by respiratory allergies such as asthma and rhinitis due to indoor and outdoor inhalant allergens (6–9). Also, sensitization to both food and inhalant allergens usually precedes or accompanies early symptoms and could be used as a risk marker to implement preventive measures (10–12). An early correct diagnosis and a subsequent optimal intervention improve the prognosis for the atopic

child with a decreased risk for future development of asthma problems (13–16). With these considerations ImmunoCAP[®] Phadiatop[®] Infant was developed. Phadiatop Infant is an *in vitro* test for graded determination of immunoglobulin E (IgE) antibodies specific to food and inhalant allergens that are relevant in the development of atopy in young children. The aim of this study was to assess the diagnostic value of Phadiatop Infant.

Methods

Study population

Children (n = 149) aged 0–4 yr with recurrent wheezing and/or eczema and no earlier diagnosis

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of allergic disease were consecutively enrolled at an allergy clinic. Approximately 75% of the children had been referred from primary care physicians to the specialist clinic for allergy assessment. The remaining 25% of the enrolled children were recruited as acutely ill patients or from wards. An assessment of atopy/non-atopy based on routine procedures at the clinic was performed for each child. The assessment comprised of case history, atopic heredity, physical examination and determination of allergen-specific IgE antibodies to food and inhalant allergens. Atopy was defined as a constitutional disposition to produce IgE antibodies to common allergens whether the child had clinical symptoms or not, as judged by the allergist. After all children had been assessed as either atopic or non-atopic, Phadiatop Infant was analyzed in a blinded manner and the allergist's assessment was used as reference to calculate the diagnostic performance characteristics of Phadiatop Infant. This study was approved by the Independent Ethics Committee of the Charité Medical University, Berlin, Germany. Informed consents were given by the parents of all children prior to enrolment in the study.

Definition of severity of symptoms

The severity of wheezing was defined as mild with the occurrence of one to two episodes during the last year, as moderate with three to five episodes during the last year and as severe with more than five episodes during the last year. The severity of eczema was defined as mild if the extent of the affected skin was less than 10% of the body, sleep was undisturbed and there was no itching, as moderate if at least one of the following criteria was fulfilled: extent 10–40%, occasional sleep disturbances or some itch during the day and as severe if at least one of the following criteria was fulfilled: extent of the affected skin more than 40%, several sleep disturbances or itching on most of the days.

Allergen-specific IgE

Serum samples were analyzed for allergen-specific IgE with Pharmacia CAP SystemTM (Phadia AB, Uppsala, Sweden). Levels ≥ 0.35 kU_A/l were considered positive. For all children, specific IgE to the following allergens were analyzed: egg white, cow's milk, wheat, peanut, soybean, timothy, common silver birch, house dust mite, cat dander and dog dander. If the case history indicated that any other allergen was involved, IgE to that allergen was also analyzed.

Phadiatop Infant

ImmunoCAP[®] Phadiatop[®] Infant (Phadia AB) is a blood test designed to detect allergen-specific IgE to food and inhalant allergens, relevant in the development of IgE-mediated disease in young children. Phadiatop Infant was analyzed quantitatively with ImmunoCAP[®] 100 (Phadia AB). The following allergens were included in the test: egg white, cow's milk, peanut, shrimp, cat epithelium and dander, dog dander, house dust mite, common silver birch, timothy, ragweed and wall pellitory. Results were expressed as Phadia Arbitrary Units/l (PAU/l) indicating the degree of sensitization. Phadiatop Infant values ≥ 0.35 PAU/l were considered positive.

Statistical analysis

For the groups of atopic and non-atopic children a descriptive analysis of demographic data was performed. The diagnostic performance of Phadiatop Infant was evaluated by calculating performance characteristics, i.e., sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals (CI). The evaluation was done using the allergist's assessment (atopic or non-atopic) as reference.

Data processing and statistical analyses were performed with the SAS[®] statistical software system.

The sum of the analysed allergen-specific IgE was calculated for each child and Spearman rank order correlation coefficients were calculated for the sum and the quantitative values of Phadiatop Infant. The relation between the assessment of the children being atopic or non-atopic and the quantitative levels of Phadiatop Infant was analyzed using a logistic regression model (17).

Results

One hundred and forty-nine children were evaluated. Fifty-three children (36%) were classified as atopic and 96 (64%) as non-atopic. The median age for the atopic children was 1.6 yr and for the non-atopic children 1.3 yr, with the youngest evaluated child being 6 wk old. One hundred and four (70%) of the evaluated children were younger than 2 yr and 45 (30%) were between 2 and 4 yr old (Table 1).

Wheezing as a single symptom was the most common symptom among the children (51%) and 12% of the children below 2 yr and 27% of the children between 2 and 4 yr were classified as atopic. The youngest wheezing child classified as

Table 1. Distribution of patients by atopic assessment, gender and age

Patient group	Total n (%)	Gender male/female n (%)	Median age, yr (min–max)
Atopic	53 (36)	34 (64)/19 (36)	1.6 (0.4–4.0)
Non-atopic	96 (64)	58 (60)/38 (40)	1.3 (0.1–4.0)
Total	149 (100)	92 (62)/57 (38)	1.4 (0.1–4.0)

atopic was 11 months old. Eczema as a single symptom was found in 28% of the children, the youngest child being 5 months old. The presence of atopy in the children with only eczema was 52% in the children below 2 yr and 50% in the children between 2 and 4 yr. Thirty-two children (21%) had a combination of several allergy-like symptoms, wheezing and/or eczema together with rhinitis, urticaria or gastrointestinal problems (Table 2).

Approximately one-third of the children with wheezing had mild symptoms, one-third had moderate symptoms and one-third had severe symptoms. The majority, 57% of the children with eczema had moderate symptoms, 31% had mild symptoms and 12% had severe eczema.

One hundred and four children (70%) had at least one atopic family member (mother, father, sibling or grandparent). The proportion was about the same for the atopic children compared with the non-atopic children, 72% and 69%, respectively. An atopic mother was reported for 64 of the children, followed by father (48/64), grandparents (33/64) and sibling (16/64).

A triggering factor, associated with the atopic symptoms, was reported for 51 children. The most common triggering factor was infection, reported for 18 children, all of whom except one were children with wheezing. The second most common triggering factor was cow's milk, reported for 16 children, 12 of whom had eczema.

Of the 41 children with only eczema 22 showed IgE antibodies to egg white, 12 to cow's milk and 8 to peanut. The most common allergens for the 76 children with only wheezing were cow's milk,

egg white and timothy present in 14, 3 and 2 children, respectively.

The performance characteristics of Phadiatop Infant in this population with a prevalence of atopy of 36% are presented in Table 3. Four children with missing Phadiatop Infant values were excluded from the analysis. The sensitivity, calculated on 145 children, was 96% (95% CI: 87–100%) and the specificity 96% (95% CI: 89–99%). The PPV and NPV were 92% (95% CI: 82–98%) and 98% (95% CI: 92–100%), respectively.

The majority of the 51 children assessed as atopic had Phadiatop Infant values in the range from 0.7 to 17.5 PAU/l. The median value was 1.99 PAU/l. The correlation between the sum of the allergen-specific IgE antibodies and the quantitative Phadiatop Infant values was for all children 0.94 ($p < 0.0001$) and for the children assessed as atopics 0.94 ($p < 0.0001$).

With the logistic regression model a curve was constructed. The shape of the curve illustrates the allergist's disposition for a positive atopy assessment as a function of the Phadiatop Infant antibody level (Fig. 1). The curve shows that in this study population the probability to be assessed as atopic increases with increasing Phadiatop Infant values.

Discussion

A statement from the pediatric section of the European Academy of Allergy and Clinical Immunology has been published with recommendations on allergy testing in children to correctly identify allergy and thereby improve the quality of care (18).

Diagnosis of IgE-mediated allergic disease in young children without objective tests could be an arbitrary process as symptoms in infancy are generally unspecific. The results from our study confirm the diagnostic value of IgE antibody measurements in addition to case history and are consistent with other findings. In a recent publication, the discrimination between IgE- and

Table 2. Symptom distribution by age group and atopic assessment

Symptom	Total n (%)	Age group		<2 yr		2–4 yr	
		<2 yr n (%)	2–4 yr n (%)	Atopic n (%)	Non-atopic n (%)	Atopic n (%)	Non-atopic n (%)
Wheezing only	76 (51)	50 (66)	26 (34)	6 (12)	6 (12)	7 (27)	19 (73)
Eczema only	41 (28)	33 (80)	8 (20)	17 (52)	17 (52)	4 (50)	4 (50)
Wheezing/eczema/other*	32 (21)	21 (66)	11 (34)	10 (48)	10 (48)	9 (82)	2 (18)
Total	149 (100)	104 (70)	45 (30)	33 (32)	33 (32)	20 (44)	25 (56)

*Wheezing and/or eczema in combination with rhinitis, urticaria or gastrointestinal problems.

Table 3. Performance characteristics of Phadiatop® Infant. All evaluated children

Phadiatop Infant test result	Atopic assessment*		Total
	Atopic	Non-atopic	
Positive	49	4	53
Negative	2	90	92
Total	51	94	145

*Atopic/non-atopic was classified according to a clinical assessment prior to Phadiatop Infant was analyzed.

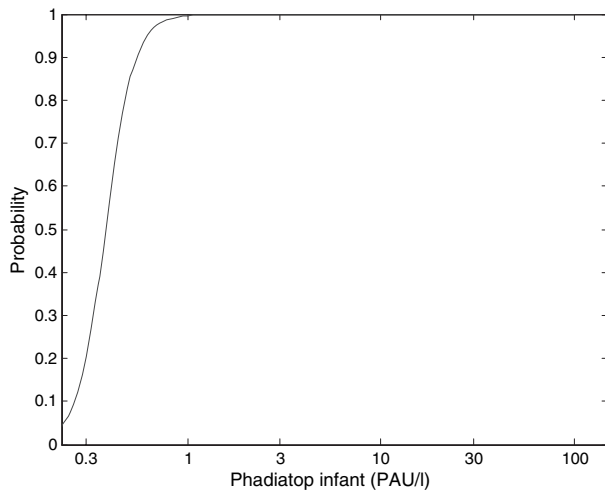


Fig. 1. The association between the quantitative levels of Phadiatop Infant (PAU/l) and the probability to be assessed as atopic.

non-IgE-mediated allergy in children 0–4 yr was strongly improved by adding allergen-specific IgE tests to history and physical examination (19). In a Dutch cohort of children below 4 yr referred to an out-patient clinic, IgE antibodies to inhalant allergens, added to history, was found a strong predisposing factor to asthma (20). Another study from a general setting in the Netherlands showed that it was possible to identify children less than 5 yr at risk for developing asthma by respiratory symptoms and subsequent testing for IgE antibodies to inhalant allergens (21).

The median age of the children in the present study was 1.4 yr and the youngest child only 6 wk. Thus, allergen-specific IgE can be detected in the circulation early in life, supporting the usefulness of testing children with allergy-like symptoms at an early age (6, 19–24). The presence of atopy in the older age group (44%) was only slightly higher compared with the younger children (32%). However, only 12% of the children younger than 2 yr with only wheezing were assessed as atopic compared with 52%

of the children with only eczema. As sensitization especially to foods occurs earlier in children with atopic dermatitis compared to children with wheeze this is not unusual. However, early sensitization to inhalants in children with atopic dermatitis predicts later allergic asthma (8, 25). An increase in atopic wheezing and a combination of several symptoms, assessed as atopic, were observed in the age group of 2–4 yr. These findings are consistent with the concept of the atopic march, beginning with eczema and continuing to respiratory symptoms, which might develop into asthma (7–9, 13). Furthermore, the common occurrence of IgE antibodies to food and particularly to egg white (54%) and cow's milk (29%) in children presenting with eczema support the atopic sensitization pattern, preceding a later sensitization to inhalant allergens and respiratory allergy (11, 26). Our results thus confirm the importance of allergy evaluation in young children with eczema at an early stage as allergy plays an important role as a trigger in this disease. A positive Phadiatop Infant test should be followed by IgE antibody testing to a selected allergen panel to verify the offending allergen(s). The panel of single allergens used in this study was a combination of the most common allergens in the northern part of Germany and chosen without knowledge of the composition of Phadiatop Infant. The different allergen-specific IgE determined with the panel and with Phadiatop Infant could in fact explain why four children were assessed as non-atopic but for whom Phadiatop Infant was positive; they might be sensitized to shrimp, ragweed or wall pellitory. In addition, the two atopic children with a negative Phadiatop Infant result but assessed as atopic might be sensitized to wheat or soybean, which is not included in Phadiatop Infant. In spite of some differences between the allergens in the panel and in the test, the results from this study show a good correlation between the sum of the single allergen-specific IgE kU_A/l levels and the Phadiatop Infant PAU/l value. The added value of quantitative IgE measurements to assess the probability of a positive diagnosis and the likelihood of clinical disease has recently been reported. Quantification of IgE antibody levels might not only be beneficial for diagnosis of allergic diseases but also serve as a marker of severity and an aid to estimate the prognosis of the disease (17, 24, 27–30).

The results from this study suggest that Phadiatop Infant can be recommended as an adjunct to the clinical information in the differential diagnosis on IgE-mediated allergy in young children. The test thus provides an

opportunity for early correct diagnosis and identification of subjects at risk for whom intervention may be necessary.

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