

Allergy screening with Phadiatop® and CAP Phadiatop® in combination with a questionnaire in adults with asthma and rhinitis

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The efficiency of the new screening tests for atopy, Phadiatop® and CAP Phadiatop®, was studied by comparing their results with a clinical diagnosis of atopy in 100 consecutive adults with asthma and/or rhinitis. Further, the diagnostic efficiency of a combination of Phadiatop and a few standardized questions was studied. The Phadiatop was found to have a specificity of 0.98, and a sensitivity of 0.92 and the CAP Phadiatop a specificity of 0.94 and a sensitivity of 0.96. When the Phadiatop was combined with a few questions, a sensitivity of 1.00 was achieved. It is concluded that Phadiatop and CAP Phadiatop have a higher diagnostic precision than other hitherto used methods for screening of atopic allergy. The place of Phadiatop in a diagnostic flow chart is suggested.

Key words: allergy; asthma; atopy; case history; diagnosis; hay fever; *in vitro* tests; Phadiatop; screening; test methods.

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CLINICAL ASPECTS

The high diagnostic efficiency of Phadiatop makes it a useful screening method for general practitioners in clinical diagnostic work. In a cost/effective diagnostic flow chart it should preferably be used in patients without a history of allergy in order to confirm a diagnosis of non-atopy, thus reducing the number of patients that must be referred for allergen-specific diagnostic testing.

Determination of total IgE has been proposed as a screening method for atopic allergy. The method, however, has very low diagnostic precision. It has been shown that RAST (18) or skin prick test (SPT) (10) with a limited number of allergens can detect most of the patients with an atopic allergy. As a consequence of these findings, a new *in vitro* test, Phadiatop® was developed (25).

Phadiatop is based on the allergosorbent principle, as is RAST, and utilizes a balanced mixture of relevant allergens causing common inhalant allergy. A further development of the method is CAP Phadiatop®. The CAP system is built around a new type of solid phase con-

sisting of a flexible hydrophilic carrier polymer encased in a CAPsule, the ImmunoCAP (2). The carrier consists of a CNB-activated cellulose derivative which can bind at least three times more protein than a corresponding paper disc and about 50 times more than can be absorbed to the inner surface of a traditional coated tube. The results of Phadiatop and CAP Phadiatop are reported as positive or negative, indicating whether or not the patients are IgE-sensitized with common inhalant allergens.

The purpose of this study was to find whether Phadiatop and CAP Phadiatop used in combination with a few standardized case history questions could have sufficient diagnostic preci-

Table 1
Patients

	Atopics	Non-atopics
Men/Women	27/26	16/31
Ages mean	28	39
range	18-56	16-65
Diagnoses		
asthma	27	15
rhinitis	49	40

sion to be used as a reliable screening method for atopy in asthma and rhinitis.

PATIENTS AND METHODS

The patients consisted of 109 consecutive adults with asthma and/or rhinitis, referred for allergy testing, 100 of whom could be classified as atopic or non-atopic after clinical investigation. Patients with isolated hypersensitivity to drugs or insect venoms were excluded. The distributions of age, sex and diagnosis are seen in Table 1.

Table 2

Results of skin prick test in 53 atopic patients

Allergen	No. positive test (> 1 +)
<i>Dermatophagoides pteronyssinus</i>	20
Horse	11
Dog	14
Cat	22
Grasses	21
Mugwort	12
Birch	23
Chironomids	12
Moulds	3

In addition to ordinary questions used in the clinical examination, patients answered a standardized questionnaire with questions presumed to have relevance for differentiating between atopics and non-atopics (8). For details, see Table 3.

In vivo tests were the skin prick test (SPT) performed with a standard allergen panel used at the clinic. The test included *D. pteronyssinus*,

Table 3
Results of answers to questions among atopics and non-atopics

Questions	Answer yes to the questions (%)		Significance of difference (χ^2)
	Non-atopics (n = 47)	Atopics (n = 53)	
Age at debut			
< 20 years	28	72	***
20-30 years	37	17	*
> 30 years	36	8	***
Periods without symptoms	49	60	ns
Symptoms worst in summer	13	57	***
Symptoms from animals	13	72	***
Symptoms when house-cleaning	13	40	**
Symptoms from work place	21	21	ns
Symptoms when eating			
nuts	11	28	*
apples	2	25	**
peaches, cherries, plums	2	15	*
carrots	0	17	**
shellfish	2	17	*
Attacks of sneezing	64	68	ns
Symptoms from strong smells	26	13	ns
More symptoms indoors	23	30	ns
More symptoms outdoors	6	28	**
Do you have an aquarium?	11	21	ns
Symptoms from any kind of hobby	4	6	ns

P* < 0.05, *P* < 0.01, ****P* < 0.001

Table 4

Comparison between clinical diagnosis and Phadiatop		
Phadiatop	Clinical diagnosis	
	Non-atopic	Atopic
Negative	46	4
Positive	1	49
Total	47	53
Diagnostic indices for Phadiatop		
Specificity		0.98
Sensitivity		0.92
Predictive value of		
neg. test (PV_{neg})		0.92
pos. test (PV_{pos})		0.98
Efficiency		0.95

horse, dog, cat, timothy, birch, mugwort (Soluprick extracts from ALK, Copenhagen, Denmark with an activity of 3 HEP), *Cladosporium*, *Alternaria* and *Aspergillus* (glycerinated extracts 1:20 w/v from the same laboratory) and a chironomid extract (red mosquito larvae 1:100 w/v, produced at Sahlgrenska sjukhuset, Göteborg, Sweden). The SPT was performed on the volar side of the forearm. A wheal reaction of the same size as that of a histamine reference (histamine 3 g/l) was recorded as 3 + . A reaction half the size of the histamine reference was recorded as 2 + . The mean ($\pm 1SD$) diameter of the wheals elicited by the histamine reference was 3.9. ± 0.9 mm.

If the patient's history indicated allergy and the result of the SPT was negative, a nasal or conjunctival provocation test was performed with non-glycerinated allergen extracts.

The physician classified the patients as atopic or non-atopic, depending on the result of case

history, SPT and, if performed, provocation test. SPT reactions of strength $\geq 2 +$ with the standardized allergen extracts were regarded as signs of atopy. If the patient had weaker reactions with such extracts or if they had isolated positive reactions with non-standardized extracts (moulds and chironomids) the results were regarded as doubtful and the patient was not included in the comparison with Phadiatop. As a consequence, 109 consecutive patients were originally tested in order to obtain 100 patients with a definitive diagnosis of atopy or non-atopy for comparison.

For *in vitro* tests a serum sample was taken during the visit to the clinic and stored at -20°C until the clinical part of the study was completed. All sera were sent to Pharmacia, Uppsala, Sweden, where they were analysed with Phadiatop and later with CAP Phadiatop according to the manufacturer's instructions. The clinical diagnoses were not known by the persons performing or recording the *in vitro* testings.

The following indices were used to characterize the *in vitro* tests:

Sensitivity: proportion of positive tests in atopics.

Specificity: proportion of negative tests in non-atopics.

Predictive value, positive (PV_{pos}): proportion of true-positive test results among all positive tests.

Predictive value, negative (PV_{neg}): proportion of true-negative test results among all negative tests.

Efficiency: the relative number of correctly classified patients.

RESULTS

According to the clinical evaluation, 53 of the patients were atopics and 47 non-atopics. The

Table 5

Details of four patients with a falsely negative Phadiatop

Patient	Age	Sex	Symptoms from		Positive skin test (allergen)	Diagnosis	
			animals	house dust		Rhinitis	Asthma
I.G.	39	F	+	+	chironomid	+	-
C.B.	17	F	+	-	cat	+	-
J.L.	31	M	+	-	DP, mugwort	+	-
L.E.	29	M	+	+	dog	+	+

DP: *Dermatophagoides pteronyssinus*

Table 6

Comparison between clinical diagnosis and history combined with Phadiatop

History	Phadiatop	Clinical diagnosis	
		Non-atopic	Atopic
+	-	6	4
+	+	0	34
-	-	40	0
-	+	1	15
Total		47	53

results of SPT in the atopic patients are shown in Table 2. The patients' answers to the questionnaire appear in Table 3. As seen from the table, answers to some of the questions differed significantly between atopic and non-atopic patients.

Of the 53 atopic patients, 49 had a positive and four a negative Phadiatop result. (Table 4). The four patients with a falsely negative Phadiatop all had a positive allergy history with, e.g. symptoms on exposure to animals (Table 5). If this information was regarded as a sign of atopy, a combination of Phadiatop and history would detect all atopic patients, i.e. the combination (history and/or Phadiatop positive) would give a sensitivity of 1.00. On the other hand, six patients (13 % of the non-atopics) would be falsely diagnosed as atopics by the history (Table 6).

The above reported results were achieved when the cut-off point between negative and positive answers of the commercially available Phadiatop was used. If a cut-off point at a 50 % lower PRU/ml-value was chosen, two of the 53 atopics had a negative test result and two of the

Table 7

Comparison between clinical diagnosis and CAP Phadiatop

CAP Phadiatop	Clinical diagnosis	
	Non-atopic	Atopic
Negative	44	2
Positive	3	51
Total	47	53
Diagnostic indices for CAP Phadiatop		
Specificity		0.94
Sensitivity		0.96
Predictive value of		
neg. test (PV _{neg})		0.96
pos. test (PV _{pos})		0.94
Efficiency		0.95

47 non-atopics a positive, which means a specificity and sensitivity of 0.96.

When the Pharmacia CAP system had been developed, the sera were also analysed with this method (Table 7). Compared with the Phadiatop, two atopics and two non-atopics converted from negative to positive (Table 8). Consequently, the sensitivity of the test rose from 0.92 with Phadiatop to 0.96 with CAP Phadiatop, whereas the specificity fell from 0.98 to 0.94.

Seven of the nine patients with doubtful clinical diagnosis had a negative Phadiatop and two a positive. With CAP Phadiatop five had a negative and four a positive atopy diagnosis.

DISCUSSION

The study showed the high diagnostic precision of the Phadiatop *in vitro* screening method, with a sensitivity of 0.92, a specificity of 0.98 and an

Table 8

Details about patients with different results of Phadiatop and CAP Phadiatop

Patient	Age	Sex	Symptom-free seasons	Symptoms from		Clinical diagnosis of atopy	Result of	
				animals	house dust		Ph	CAP Ph
I.G.	40	F	-	+	+	+	-	+
L.E.	30	M	-	+	+	+	-	+
P.G.	23	M	+	+	-	-	-	+
N.E.	37	M	-	-	-	-	-	+

Ph: Phadiatop

Table 9
Diagnostic indices of Phadiatop according to reported studies, comprising 2,700 patients

Authors	No.	Sens.	Spec.	Efficiency
Anichini et al. (1)	110	0.88	0.90	0.89
Betti et al. (3)	98	0.87	1.00	0.92
Biot et al. (4)	109	0.88	0.88	0.88
Bonini et al. (5)	100	0.93	0.97	0.96
Carrodus & Tiernan (6)	118	0.91	0.98	0.94
Crimi et al. (7)	121	1.00	0.93	0.98
Duc et al. (9)	100	0.94	1.00	0.96
Ebner et al. (10)	73	0.98	0.83	0.93
Eriksson (present study)	100	0.92	0.98	0.95
Guillou et al. (13)	105	0.96	1.00	0.98
Guillou et al. (14)	212	0.88	0.82	0.85
Gustafsson et al. (15)	100	0.95	1.00	0.97
Herkert et al. (16)	133	0.84	1.00	0.91
Herold et al. (17)	100	0.96	0.96	0.96
Loidolt (18)	101	0.72	0.81	0.75
Ribeiro et al. (20)	98	0.93	0.93	0.93
Segalen et al. (21)	185	0.94	0.83	0.93
Treden et al. (2)	201	0.95	0.92	0.94
Wever et al. (23)	248	0.96	1.00	0.99
Wüthrich (24)	88	0.75	0.91	0.85
Zetterström et al. (26)	200	0.92	0.95	0.94
Mean		0.91	0.93	0.92
SD		0.07	0.07	0.06

efficiency of 0.95. The diagnostic precision of Phadiatop found in this study is in agreement with that found by other authors (Table 9). Phadiatop thus has a higher diagnostic precision than methods hitherto used for screening of atopy.

The diagnostic precision of CAP Phadiatop and Phadiatop was roughly the same. However, sensitivity was somewhat higher (0.96) and specificity somewhat lower (0.94) with CAP Phadiatop. Zetterström et al. (27) found both sensitivity and specificity higher with CAP Phadiatop compared with Phadiatop: 0.97 sensitivity and 1.00 specificity with CAP Phadiatop and 0.92 and 0.95, respectively, with Phadiatop.

In clinical diagnostics, a patient history is the first step and should always be included in the diagnostic consideration. In accordance with another study (8) this study showed that positive answers to some questions strongly indicate atopy: early debut of asthma or rhinitis, seasonal symptoms in summer, symptoms on contact with animals or when house-cleaning, as well as

symptoms when eating birch-pollen related foods (12).

All patients with a falsely negative Phadiatop had a history indicating animal allergy. If this information was regarded as a sign of atopy, then a combination of Phadiatop and history (one or both positive) would give a sensitivity of 1.00. However, in such a case, 13 % of the non-atopic patients would be falsely diagnosed as atopics.

In clinical work with adult patients with asthma and rhinitis a common problem is to differentiate an atopic (i.e. caused by specific IgE allergy) from a non-atopic disease. For atopics an allergological investigation could be useful, since allergen-specific therapy (elimination or desensitization) might improve their disease. *In vitro* allergy testing using, e.g. RAST with several allergens, is expensive. For this reason a reliable screening test would be helpful.

A screening method used in primary health care for determining whether or not patients must be referred for further evaluation should have high sensitivity (and a high PV_{neg}). In

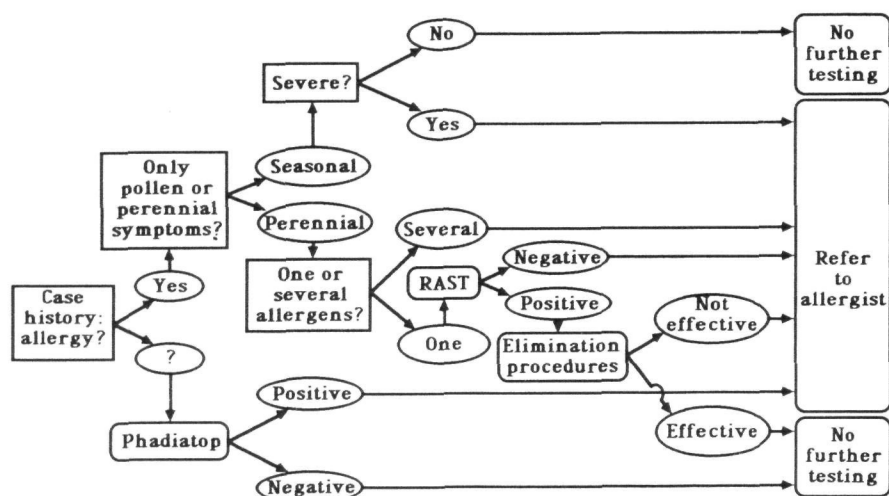


Fig. 1. Flow chart for a cost-effective allergy diagnosis.

other words, the physician and the patient must feel confident that an allergy is not overlooked. The specificity of the test (and the PV_{pos}) does not need to be 100 % since the consequence of a falsely positive test will only be that the physician refers a non-atopic patient for allergy diagnosis. For this reason, in clinical work the Phadiatop test should be used in combination with case history since, according to the results of this study, such a combination gives very high sensitivity.

When should Phadiatop and other in vitro methods be used in clinical diagnostics?

Since Phadiatop is a screening test there is no reason to use it in combination with an allergen-specific diagnostic method. The Phadiatop should be used by the GP to select which patients should be referred for specific allergy testing. If the patient's history gives suspicion of specific allergy, then Phadiatop should not be used but the patient referred for testing with other methods. Patients deteriorating on contact with furry animals, cleaning the house, eating pollen-related foods (12), as well as patients with seasonal symptoms from pollens, must be regarded as potentially atopic, regardless of the Phadiatop result. Thus, in such cases there is no reason to use Phadiatop. In those cases when the history is doubtful, Phadiatop should be used as a screening method for finding out which patients do not need referral for allergen-specific testing.

A flow chart for a cost-effective allergy diagnosis in primary care is proposed in Fig 1. The allergy work-up starts with a careful case history. If an allergy is suspected, then further steps depend on whether the patient has a seasonal rhinitis/asthma (i.e. pollen allergy) or a perennial. In pollen allergy, the only allergen-specific therapy is desensitization. Such a therapy is indicated only in patients who suffer in spite of more simple treatment, such as antihistamines and nasal corticoid spray. Thus, allergen-specific diagnosis is only necessary in more severe cases, when desensitization therapy is being considered.

In perennial disease, further steps depend on whether one allergen or several allergens are suspected as etiological agents. If only one allergen (usually a domestic animal) is suspected, then a RAST with the relevant allergen could be a cost-effective method. If RAST proves positive, then, hopefully, the patient will accept eliminating the offending animal in order to avoid symptoms. If, however, RAST is negative, in spite of a positive history, then the patient should be referred for further allergy testing. In patients with perennial symptoms and suspicion of allergy to several allergens the most cost-effective procedure is to perform a SPT, since RAST is an expensive method when used for several allergens. Such patients should preferably be referred to an allergy unit for further testing.

The Phadiatop should be used in patients with a negative or doubtful history. If Phadiatop in such patients proves negative, then no further diagnostic measures are necessary – the patient is non-atopic. If Phadiatop is positive, the patient should be referred for further evaluation.

It should be emphasized that this flow chart deals only with the allergy diagnosis. Patients with severe disease, whether atopic or non-atopic, should of course be referred to a specialist.

In conclusion, Phadiatop has a higher diagnostic precision than methods hitherto used for screening of atopic allergy. If wisely used it could be a cost-saving measure in allergy diagnosis.

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