

Short communication

Current allergic asthma and rhinitis: diagnostic efficiency of three commonly used atopic markers (IgE, skin prick tests, and Phadiatop[®])

Results from 8329 randomized adults from the SAPALDIA study

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Total serum IgE, Phadiatop[®], and the skin prick test (SPT) are commonly used to diagnose atopic diseases. However, no large study has ever been done to test their diagnostic efficiency. We studied the diagnostic value of these three atopic markers in 8329 well-randomized adults from the Swiss Population Registry. The prevalence of current allergic asthma (CAA) was 1.8% and of current allergic rhinitis (CAR) 16.3%. The prevalences of positive Phadiatop, positive SPT (at least, one out of eight SPT to common aeroallergens with a wheal of ≥ 3 mm), and positive total IgE (IgE ≥ 100 kU/l) were 29, 23, and 23%, respectively. To diagnose CAA and CAR, the sensitivity of Phadiatop was significantly higher than that of SPT (72.5% vs 65.4%, 77.1% vs 68.4% respectively; $P < 0.01$ and < 0.001) and IgE (72.5% vs 56.9%, 77.1% vs 43.9%, respectively; both $P < 0.001$). The sensitivity of SPT was significantly higher (68.4% vs 43.9% $P < 0.001$) than that of IgE to diagnose CAR. When CAA and CAR were excluded, the SPT specificity was significantly higher than that of Phadiatop (77.8% vs 71.9% and 85.9% vs 80.5%, respectively; both $P < 0.001$): when CAR was excluded, SPT was significantly higher than IgE (85.9 vs 81.4%; $P < 0.001$). SPT had significantly the best positive predictive value for CAA (5.2% for SPT vs 4.6% for both IgE and Phadiatop; both $P < 0.001$) and CAR (48.7% for SPT vs 43.5% for Phadiatop and 31.6% for IgE; both $P < 0.001$). The three markers of atopy had roughly the same negative predictive value (NPV) for CAA, but IgE had a significantly lower NPV for CAR than SPT and Phadiatop (88.1% vs 93.3% and 94.7%, respectively; both $P < 0.001$). The diagnostic efficiency of SPT was significantly higher than that of Phadiatop (83.1% vs 79.9% and 77.6 vs 71.9%, respectively; both $P < 0.001$) to diagnose CAR and CAA. IgE and SPT had equal efficiency (77.6%), which was significantly higher than that of Phadiatop, to diagnose CAA (71.9%; both $P < 0.001$). In conclusion, SPT have the best positive predictive value and the best efficiency to diagnose respiratory atopic diseases. Furthermore, SPT give information on sensitivity to individual allergens and should therefore be used primarily by clinicians to assess respiratory allergic diseases. Moreover, they are cheaper and provide immediate, educational information for both patient and physician.

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Atopy is generally defined as an inherited predisposition to produce abnormal amounts of immunoglobulin E (IgE) in response to contact with aeroallergens (1). It can be demonstrated by skin prick tests (SPT) or increase in IgE measured as serum total IgE or specific IgE. There have been many studies on the diagnostic value of these atopic markers (2–6) which used different definitions of atopic markers or atopic diseases, and which were carried out in small or poorly randomized samples of the population, leading to selection bias with false prior probability of having the allergic disease (7). Moreover, SPT and laboratory methods for the measurement of IgE are far from being well standardized (8).

We recently undertook a large epidemiologic survey (9, 10) of the prevalence of respiratory diseases and these three atopic markers in a randomized sample of the Swiss population, and we were able to study the value of these markers to diagnose current allergic asthma or rhinitis by using standardized *in vitro* and *in vivo* allergologic methods and following the recommended cutoff values for atopic markers (11, 12).

Material and methods

Subjects

Our data are part of the SAPALDIA study (Swiss Study on Air Pollution and Lung Diseases in Adults). First we randomly selected 17 300 subjects aged 18–60 years from resident lists of eight different areas of Switzerland, of whom 9651 (adjusted participation rate 59%) agreed to participate in the present study. There were no marked differences in demographic data (age, race, sex, social status, etc.) or prevalence of self-reported symptoms between people taking part or not taking part in the study (9, 10). The recruitment and survey of subjects were equally distributed over a 12-month period to avoid as much as possible seasonal variations in environmental or intrasubject factors. All subjects who had not properly undertaken the three atopic tests (total IgE, SPT, and Phadiatop®) were excluded, leaving 8329 subjects for the present analysis.

Atopic markers

Total serum IgE was measured with the CAP FEIA technology (Pharmacia®, Uppsala, Sweden) in duplicates and considered positive if its value was ≥ 100 kU/l (13). SPT to glycerol (negative control), histamine (positive control), and eight aeroallergens (cat, dog, *Dermatophagoides pteronyssinus*, grass, birch, *Parietaria*, *Alternaria tenuis*, and *Cladosporium*) were performed with Phazet®

lancets (Pharmacia) on the volar side of the forearm, according to the instructions of the European Respiratory Health Survey, by specially trained fieldworkers (physicians and nurses under the supervision of the local chief investigator). The SPT reactions were read after 10 min for histamine and after 15 min for allergens. The perimeters of the wheals were traced with a fine-point pen and transferred by Scotch tape to the SPT protocol sheet. The largest and the smallest diameters of the wheals were measured. For evaluation of the responses to allergens, the difference between the mean wheal diameter (i.e., the mean of the largest and the smallest wheal diameter) and the mean diameter of the negative control wheal was computed. The SPT was considered positive if the wheal diameter of at least one allergen was ≥ 3 mm, according to the recommendations of the European Academy of Allergology and Clinical Immunology (12).

By fluoroenzyme immunoassay, Phadiatop detects the presence of specific serum IgE against common inhalant allergens (pollens, house-dust mite, molds, and mammals). The percentage binding of the Phadiatop was determined, and the results were classified as positive or negative when the absorbance result was above or below the reference serum value.

Definitions

The diagnosis of asthma and rhinitis was based on a standardized questionnaire (9), and asthma was defined in three steps:

- 1) *Doctor-diagnosed asthma* (DA) was defined as a positive answer to the following two questions, "Have you ever had asthma?" and "Was this confirmed by a doctor?"
- 2) *Current asthma* (CA) was defined as DA and a positive answer to the following question, "In the last 12 months, have you had at least one attack of asthma?"
- 3) *Current allergic asthma* (CAA) was defined as CA and the presence in the last 12 months of respiratory symptoms (wheezing, dyspnea, or cough) or rhinoconjunctivitis related to common allergen exposure (mammals, feathers, house dust, trees, plants, or flowers).
- 4) *Current allergic rhinitis* (CAR), with or without conjunctivitis, was defined as a positive answer to both of the following questions, "In the last 12 months, did you suffer from allergic rhinitis, including hay fever" and "Did you experience a runny or stuffy nose, the urge to sneeze, or itchy or watery eyes related to common allergen exposure?"

5) *Current allergic disease (CAD)* was defined as the condition of subjects who had either CAA or CAR, or both allergic diseases.

Sensitivity was defined as the proportion of positive atopic tests in CAA and/or CAR; *specificity* as the proportion of negative atopic tests in non-CAA and/or non-CAR; *positive predictive value (PPV)* as the proportion of true-positive test results among all positive tests; *negative predictive value (NPV)* as the proportion of true-negative test results among all negative tests (14); *efficiency* as the rate of true-positive and true-negative subjects divided by all the subjects; i.e., the percentage of correctly classified patients.

Statistical analysis

We used the statistical software SAS. The statistical significance of differences in sensitivity, specificity, and efficiency was assessed by the McNemar test. To assess the statistical significance of differences in PPV and NPV, these differences were Studentized (i.e., divided by their estimated standard errors [SE]) and compared with the quantiles of the standard normal distribution (15). To estimate the standard error of ΔPPV ($= PPV_2 - PPV_1$), this difference was decomposed into three summands ΔPPV_1 , ΔPPV_2 , and ΔPPV_3 , each one representing the contribution to ΔPPV from one of the subsamples "both tests positive", "only the first test positive", and "only the second test positive". For the following computations, the sizes of these subsamples were assumed to be fixed, an assumption which may have slightly underestimated the true standard errors. The standard error of ΔPPV was then calculated by taking the square root of the sum of $SE(\Delta PPV_1)^2$, $SE(\Delta PPV_2)^2$, and $SE(\Delta PPV_3)^2$. Since, under the above assumption, each of the ΔPPV_i could be expressed as a fixed multiple of a binomially distributed variable, these latter standard errors could easily be estimated. The statistical significance of differences in NPV was assessed in an analogous way.

Results

Prevalence of allergic diseases and atopic markers

The prevalence of respiratory allergic diseases and positive atopic markers is reported in Table 1. Out of 1361 subjects with CAR and 153 subjects with CAA, 92/153 (60%) subjects simultaneously had CAA and CAR. Phadiatop was positive in 2410/8329 subjects (29%); 1912/8329 (23%) subjects had at least one positive SPT, and 1890/8329 (22.7%) had total IgE of ≥ 100 kU/l.

Table 1. Prevalence of allergic respiratory diseases and atopic markers in 8329 subjects

	n	Prevalence	CI
DA	566	6.8%	6.3–7.30
CA	208	2.5%	2.2–2.80
CAA	153	1.8%	1.5–2.10
CAR	1361	16.3%	15.5–17.1
CAA and/or CAR	1422	17.1%	16.3–17.9
Phadiatop®	2410	28.9%	28.0–29.9
Positive SPT	1912	23%	22.1–23.9
IgE ≥ 100 kU/l	1890	22.7%	21.8–23.6

CI: 95% confidence interval; DA: doctor-diagnosed asthma; CA: current asthma; CAA: current allergic asthma; CAR: current allergic rhinitis; SPT: skin prick test.

Diagnostic value of atopic markers for CAA, CAR, or CAD (Table 2)

Phadiatop was significantly more sensitive than SPT and IgE to diagnose CAA and CAR or CAD, whereas SPT was significantly more sensitive than IgE to diagnose CAR or CAD. On the other hand, SPT was significantly more specific than Phadiatop to exclude CAA, CAR, or CAD. It was also significantly more specific than IgE to exclude CAR or CAD. However, there was no significant difference in the specificity between SPT and IgE to exclude CAA and between Phadiatop and IgE to exclude CAR or CAD. SPT had significantly the best PPV for CAA, CAR, or CAD. The three atopic markers had quite the same NPV for CAA, but IgE had a significantly lower NPV for CAR and CAD than the two other atopic markers.

As for the efficiency of the tests, SPT and IgE were significantly better than Phadiatop for CAA. SPT was significantly the most efficient test for CAR and CAD.

Discussion

This study shows that there are real differences in the diagnostic value of the three most commonly used atopic markers to assess allergic asthma and rhinitis. The sensitivity of Phadiatop was significantly higher than SPT and IgE. The best specificity was obtained by SPT. However, these differences, although statistically significant, are not necessarily clinically relevant. Sensitivity and specificity give incomplete and sometimes ambiguous information about the diagnostic value of a test, as discussed by Wulff (16). It is important to look at the reliability of a positive or negative test; i.e., its PPV and NPV and its diagnostic efficiency. The best PPV to diagnose CAA and/or CAR was obtained by SPT, whereas the NPV was the same between Phadiatop and SPT and lower for IgE. Finally, SPT

Table 2. Value of atopic markers to diagnose CAA, CAR, or CAD

		Sensitivity (%)		Specificity (%)		Positive predictive value (%)		Negative predictive value (%)		Efficiency (%)
CAA	Phad	72.5	***	71.9	***	4.6	**	99.3	***	71.9
	SPT	65.4		77.8		5.2		99.2		77.6
	IgE	56.9		77.9		4.6		99.0		77.6
CAR	Phad	77.1	***	80.5	***	43.5	***	94.7	***	79.9
	SPT	68.4		85.9		48.7		93.3		83.1
	IgE	43.9		81.4		31.6		88.1		75.3
CAD	Phad	76.1	***	80.8	***	44.9	***	94.3	***	80.0
	SPT	67.4		86.2		50.2		92.8		83.0
	IgE	44.0		81.7		33.1		87.6		75.2

CAA: current allergic asthma; CAR: current allergic rhinitis; CAD: CAA and/or CAR; Phad: Phadiatop; SPT: skin prick test. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

was the most efficient test to diagnose CAA and/or CAR.

As expected, the prevalence of atopy and atopic diseases, such as CAA and CAR, is high in the general population. Matricardi et al. (6) found a prevalence of atopy of 20% as measured by positive Phadiatop. Surprisingly, they did not describe the criteria of the medical history used to diagnose allergic asthma or rhinitis. Vervloet et al. (17), who also did a large epidemiologic survey in 2067 adults, found a cumulative prevalence of 18.5% for hay fever, 5.5% for asthma, and 20% for positive Phadiatop. To study the diagnostic value of atopic markers, we decided to look only at the current prevalence of allergic asthma or rhinitis for two reasons. First, the duration of symptoms of asthma or hay fever varies greatly throughout life (18), and defining as "diseased subjects" those without CAA or CAR for many years would introduce an important bias because there would be a high proportion of subjects with a positive test and no real clinical disease. Second, one of the most frequent decisions a clinician makes is whether to order a test to diagnose a current disease, i.e., CAA or CAR, and not a previous disease or a risk factor for allergic disease. In other words, when dealing with the diagnostic value of atopic markers in atopic diseases, there is a high rate of anticipated false-positive results. Surprisingly, we could not find any study (2–4, 10, 17, 19, 20) with such a clear definition of CAA or CAR when testing the diagnostic value of atopic markers for allergic diseases even though Weinstein & Fineberg (21) clearly emphasized the importance of defining the "disease" when studying the value of diagnostic tests.

Our definition of current asthma based on a questionnaire could be considered too restrictive, as subjects were defined as current allergic asthmatics only if they had presented at least one attack of asthma during the last 12 months. Using a similar

definition of CAA (over the last 12 months, ≥ 1 attack of dyspnea or wheezing), Norrman et al. (22) found a slightly higher prevalence of CAA (2.8% in a sample of 1100 subjects), a finding which can easily be explained by the younger age of their population sample (mean age: 14 years). It is well known that many asthmatic children grow out of asthma (18) and that the prevalence of asthma is lower in adults. On the other hand, we do not think that symptomatic asthmatic patients were missed because asthma instability is a nosologic prerequisite in the definition of this disease (23), although we admit that we could have missed some patients who expressed their allergic disease especially by rhinoconjunctivitis rather than by asthma with very mild and quickly forgotten symptoms. The percentage of atopic asthmatics among all current asthmatics is similar to that in another study which found 87% of atopic asthma, as defined by positive SPT and positive history, among 127 current asthmatics (24). One could argue that we should define asthma by a more specific test, rather than by using symptoms. As recently stressed by Woolcock (1), there is no satisfactory definition of asthma, and it is not yet possible to have a specific and measurable marker of asthma. In our large epidemiologic survey, we systematically measured bronchial reactivity to methacholine, and we could have easily integrated bronchial hyperresponsiveness (BHR) in the definition of asthma. However, asthma cannot be defined as BHR because abnormal responses are found in normal persons without symptoms (25, 26) and in patients with other diseases, especially chronic obstructive pulmonary disease (27, 28).

The value of any diagnostic test depends not only on the definition of disease but the level of the cut-off point. To test the diagnostic value of atopic markers by well-known and accepted criteria, we used well-standardized cutoff points to define positive Phadiatop, SPT, or IgE (12, 13, 22, 29). It is

interesting that we could recently suggest that an IgE level of 100 kU/l may be a good cutoff point to study respiratory atopic diseases (29). The exact composition of the inhalant allergens present in the Phadiatop is not declared by the manufacturer. Therefore, it might be difficult to compare Phadiatop with other tests, as the prevalence of allergens is different according to the geographic area where the test is performed. In a random sample of 100 sera, Wüthrich et al. (10) have already compared the results obtained by Phadiatop with the Multi-RAST screen Sx₁, which detects the presence of specific serum IgE against well-defined inhalant allergens, and found results very comparable with those obtained by Phadiatop independently of the different area of the SAPALDIA study. Thus, we can assume that Phadiatop contains at least these eight allergens, as in the SPT, and that a comparison between the three atopic markers is reasonable. Unlike Phadiatop, Phazet is no longer available in Switzerland. However, as already discussed (10), the potency of Phazet is equivalent to that of SPT extracts if the technique is well standardized. Therefore, we believe that our results remain true when conventional prick tests are used with the proper technique.

Compared to other studies (3, 6, 20), the PPV of atopic markers was low in our study. This is due to the relatively low prevalence of respiratory allergic diseases in a representative sample of the general population compared to a selected sample of patients attending an allergic clinic.

In conclusion, this study, based on a very large randomized sample of the adult population, clearly demonstrates that SPT have the best PPV and the best efficiency to diagnose current respiratory allergic diseases. Total IgEs have a lower diagnostic value than SPT and Phadiatop.

Allergy skin testing should be used more frequently by experienced clinicians. It is simple, cheaper, and more informative than the two other atopic markers. It not only gives immediate information on specific allergens but also provides immediately a clear illustration to the patient, which may reinforce educational messages about the allergic disease and the necessity of avoidance measures (11). *In vitro* tests should be preferred as an alternative only in primary care settings where staff are not well trained to do SPT.

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