

Diagnosis of IgE-mediated allergy in the upper respiratory tract

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A statistical analysis was made of data concerning diagnosis of IgE-mediated allergy in the upper respiratory tract in 292 patients. A study was made of: skin test, total and specific IgE (RAST), X-sinus, red blood investigation, and cytology of nasal smear. It appears that screening for the presence of an IgE-mediated allergy in the upper respiratory tract can be performed efficiently with a limited number of skin tests (rye grass, timothy, birch, house dust mite and cat). In this study a greater number of skin tests (15 instead of 5) yielded little additional information (in 2% of the patients). A rather poor correlation between skin test and RAST was found.

Key words IgE mediated allergy; screening; upper respiratory tract.

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CLINICAL ASPECTS

This paper describes the value of several frequently used tests in patients, in whom an IgE-mediated allergy of the upper respiratory tract is suspected. Based on the findings, a simplified protocol is suggested which can be used for screening for an IgE-mediated allergy in an ENT practice.

Allergy is a frequently occurring disease: 10-15% of the Dutch population suffers from an IgE-mediated allergy (formerly known as type I hypersensitivity) (2), leading to allergic rhinitis and bronchial asthma. This percentage seems to increase. The incidence of allergy in a general practice is 7.3 per 1000 per annum, the prevalence is 12% (8). The diagnostic procedures and treatment of allergic upper airway diseases involve considerable cost to Public Health.

The presence of an IgE-mediated allergy is primarily investigated with skin tests (bio-assay) and determination of specific antibodies (immunoassay): total IgE and specific IgE (RAST). Moreover, it is possible to look for the number of eosinophilic granulocytes in blood and nasal smear, to perform nasal and bronchial provocation tests and to use more advanced investiga-

tions, such as the capacity of basophilic granulocytes to liberate histamine.

In this study we investigated the efficiency and mutual agreement of several tests to demonstrate an IgE-mediated allergy in the upper respiratory tract. On the basis of our results we propose an effective and economic screening method for the presence of an IgE-mediated allergy in the upper respiratory tract.

PATIENTS AND METHODS

From a total of 830 we chose at random 292 patients visiting the outpatient department of allergy and the department of otorhinolaryngology and head and neck surgery for the first time in 1985. All patients complained of upper air-

Table 1.
Results of the percutaneous skin test

	Negative (%)	Questionable (%)	Positive (%)	No. people tested
Summer pollen				
rye grass	73.2	4.1	22.7	290
timothy	72.5	6.2	21.3	290
rye	75.0	4.7	20.3	275
Yorkshire fog	73.6	5.8	20.6	275
Spring pollen				
alder	84.1	5.1	10.8	275
birch	77.2	6.6	16.2	288
hazel	85.6	5.4	9.0	276
oak	90.6	4.3	5.1	275
Autumn pollen				
mugwort	91.6	4.4	4.0	273
plantain	82.2	8.4	9.4	273
Mite				
house dust mite	48.3	8.0	43.7	287
storage mite	55.4	9.8	34.8	275
Domestic animals				
cat	67.4	11.8	20.8	287
dog	67.5	18.5	14.0	285
horse	88.5	7.9	3.6	278

ways problems, possibly caused by allergy. The selection has been arranged such that the number of patients participating corresponded to the number of the entire group in any given month.

Patients were examined for the presence of an IgE-mediated allergy in the upper airways as frequently as possible according to a fixed protocol: medical history, ENT examination, percutaneous skin tests with 100,000 BU/ml extracts (Pharmacia), determination of total IgE and specific IgE (RAST, Pharmacia, expressed in PRU/ml = Phadebas RAST Unit/ml), red blood investigation, cytology of nasal smear, X-ray studies of the sinuses (Waters, Caldwell) and, depending on the presence of lower respiratory tract complaints, lung function tests

(Gould spirometer). Skin tests were performed with a series of at least 15 allergens and two control tests, namely histamine and solvent.

Patients with a negative reaction to histamine ($n = 2$) were excluded from these studies. The skin tests of patients with positive reactions to the solvent were corrected. Skin tests were always done and evaluated by the same person (no reaction = 0; reaction 2 mm diameter = 1+; 4 mm = 2+; 6 mm = 3+ and 8 mm or more = 4+). A positive RAST was classified as Group 2 (0.76–2.99 PRU/ml) up to and including Group 4 (> 17.5 PRU/ml), a questionable RAST as Group 1 (0.35–0.75 PRU/ml) and a negative RAST was equal to Group 0 (0–0.35 PRU/ml). Red blood investigation included ESR, Hb, Ht, leucocytes and eosinophils. The number of eosinophils in the nasal smear was divided into three categories: no, few or many eosinophils. For statistical analysis the Kruskal-Wallis test and the chi-square test for contingency tables were used to test the hypotheses.

The following parameters were studied:

- a) results of skin tests
- b) relation between skin tests and total IgE
- c) relation between skin tests and specific IgE (RAST)
- d) results of red blood investigation
- e) relation between skin tests and nasal smear

RESULTS

Skin tests

Results of skin tests are given in Table 1. A positive reaction corresponds to a skin reaction 2+, 3+ or 4+, a questionable reaction to 1+, whereas a negative reaction equals no skin reaction (0).

The distribution of different grass pollen proved to be equal: 21.2% of all persons tested had a positive reaction. Of the tree pollen investigated, birch yielded the highest percentage of positive reactions (16.2%). There were only a few positive reactions to weed pollen, predominantly mugwort (4.0%). Most positive reac-

tions were seen to house dust mite (*D. pteronyssinus*) (43.7%) and storage mite (*D. farinae*) (34.8%). Among domestic animals the cat yielded most positive reactions (20.8%).

Using those allergens with the most frequent positive skin reactions we compiled a "limited" skin test consisting of rye grass, timothy, birch, house dust mite and cat. 282 patients (97.2%) were tested for this combination of 5 allergens, henceforth called "limited number". The data of this limited number were recorded as follows: all reactions negative = negative, no positive reactions but at least 1 questionable = questionable; at least 1 positive reaction = positive. Of these patients 34.6% showed a negative, 9.2% a questionable and 56.2% a positive skin test.

Using the limited number (7 instead of 17 skin tests) we found that 2.0% of all patients with a negative limited number of skin tests ($n = 99$) showed a positive reaction in the extended number of tests (2 patients had positive reactions (3+) to *D. farinae*).

Retrospectively, 14.3% of all patients with negative reactions to the limited number of skin tests showed one or more positive reactions to specific IgE (RAST). In these cases the RAST scored 22 times 2+ and four times 3+; specific IgE to cat scored most frequently positive (6 ×).

In the remainder of this study, only results of the combined 5 skin tests are used.

Skin tests and total IgE

Table 2 presents the relation between the serum total IgE and the results of the combined skin tests. To reduce the influence of some extremely high IgE values, median values of IgE instead of mean values are shown. Patients have been divided into three age groups. There was a positive

Table 3.

Relation between skin tests and specific IgE for rye grass			
Specific IgE (RAST)	Negative	Questionable	Positive
Negative (Group 0)	175	5	4
Questionable (Group 1)	11	0	2
Positive (Groups 2-4)	12	4	55

correlation between serum total IgE levels and positive reactions to the combined skin test ($P < 0.0001$ Kruskal-Wallis test). High IgE values were specifically found in the 10-15 year age group, not only concerning median values but also minimal and maximal values of total IgE.

Skin tests and RAST

The degree of agreement between the five skin tests and the values of corresponding specific IgE (RAST) is studied using the so-called kappa-coefficient. The value of this kappa-coefficient indicates the agreement between the two tests: +1 indicates a total agreement, 0 indicates that the agreement is purely by chance (13).

The highest value was found for timothy (0.70), the lowest for cat (0.38). The values for house dust mite, rye grass and birch were 0.69, 0.67 and 0.49, respectively. It is generally accepted that a kappa-coefficient of ≥ 0.8 represents good agreement between two tests. It appears that the agreement between skin test and specific IgE was poor in all cases. The reason for this varied per allergen. For instance, the skin test values and specific IgE for rye grass in Table 3. With complete agreement between skin test and

Table 2.

Relation between skin tests and median values of the serum total IgE (U/ml) in 3 age groups

	Negative	Questionable	Positive
≤ 9 years	68.5	43.0	190.0
10-15 years	112.0	645.0	640.0
≥ 16 years	20.5	148.0	180.0

Table 4.

Red blood investigation

	No. people tested	Abnormal (%)
ESR (normal < 20 mm/h)	270	7.8
Hb (normal > 8 mmol/l)	271	20.7
Hct (normal > 0.04)	268	16.8
Leucocytes (normal $< 10 \cdot 10^9/l$)	267	4.5
Eosinophils (normal $< 0.40 \cdot 10^9/l$)	246	11.8

specific IgE all values should stand on the depicted bevel line. This was only partly true. The kappa-coefficient of rye grass (0.67) points to some agreement. According to Table 3, the specific IgE for rye grass frequently scored higher than the skin test. The same tendency was found for timothy and house dust mite. For birch, the skin test frequently scored higher than the corresponding specific IgE. For cat, the agreement between skin test and specific IgE was very poor: sometimes the skin test scoring higher values, sometimes the opposite.

Red blood investigation

Table 4 is a summary of the routine hematological study, divided according to standard values used in our hospital. The division of normal and abnormal values was studied for groups of patients with a positive, a questionable, or a negative limited number of skin tests. The division of normal and abnormal values of ESR, Hb and Hct yielded no relation with the skin tests results. The number of leucocytes and eosinophils showed some relation. Elevated leucocytes was significantly associated with a negative or a questionable skin test ($P = 0.0241 \chi^2$ test). In the group with a negative or questionable skin test 7.1% showed increase in leucocytes; in combination with a positive skin test this occurred in only 2.7% of all cases.

Elevated eosinophils was significantly associated with a questionable or positive skin test ($P = 0.0005$), (χ^2 test). In these two groups increased eosinophils was found in 17.0%, whereas a negative skin test was never accompanied by an increased eosinophil count, not even in children. The numbers of eosinophils (normal or abnormal) were compared in three different age groups (< 10 years, 10-15 year and > 15 years). An abnormal (= elevated) number of eosinophils significantly diminishes with increasing age groups ($P = 0.0006$ Kruskal/Wallis test).

Skin test and cytology of nasal smear

The findings of cytological investigations of nasal smear have been studied in relation to the

results of the limited number of skin tests. A group of 197 patients could be evaluated. A high eosinophil count in nasal smear was found more frequently in patients with a positive skin test (33.3%) than in those with a negative (10.8%). This association was significant ($P = 0.0159 \chi^2$ test).

DISCUSSION

Allergic rhinitis together with asthma and atopic dermatitis form "the atopic syndrome". To a general practitioner diagnosing the atopic syndrome, medical history is the most important source of information; this history determines whether further investigations are needed and where they should be done (2). In this study all patients had a positive history of allergy. Being a retrospective study, it was impossible to reassess these complaints in more detail.

Further investigation (identification of the responsible allergens) can be done in two ways: skin tests (bio-assay) and determination of specific IgE (RAST/immuno-assay). Both tests are equally informative, the choice between them is based on practical reasons (2)

Advantages of the skin test are:

- Usually higher sensitivity, differing between allergen extracts (10, 11, 14).
- the results of the test are known after 20 min
- in some patients the immunological effect of hyposensitization can be assessed on the basis of the late skin reactions
- skin test with an extended series of allergens can detect early stage - sensitizations and thus have a preventive effect (4)
- using several dilutions, i.e. skin tests can give an idea of the intensity of sensitization
- often less expensive than immunoassay

Disadvantages of the skin tests are:

- not suitable with eczema, dermatography or strong pigmentation
- usually badly tolerated by young children
- influenced by other drugs, particularly antihistamines and high doses of corticosteroids (12)

This study shows that a limited number of skin tests with five allergens (rye grass, timothy, birch, house dust mite and cat) and two controls (histamine and solvent) appear to be efficient. In comparison with the complete collection of skin tests, consisting of 15 allergens, only 2.0% of positive skin tests are missed by patients with negative limited number of skin tests. Eriksson et al. (6) concluded that three allergens (timothy, house dust mite and cat) were sufficient to detect 85% of the atopic patients with asthma or rhinitis; 98% of the patients with a seasonal allergy responded to at least one of the skin tests, consisting of timothy, birch and mugwort. It appeared that, using this limited number, determination of specific IgE (RAST) yielded additional information in 14.3%. RAST appears indicated only when skin tests are difficult to perform.

There is a strikingly small agreement between skin tests and specific IgE, particularly for cat dander. It must be borne in mind that skin tests concern the tissue (mast-cell bound IgE), whereas RAST concerns serum, (free circulating IgE). Further, agreement between the tests depends partly on the definition of a positive skin test. Fimmerty et al. (7) noted an increasing overall agreement between specific IgE and skin test when a positive skin test was defined as having a diameter ≥ 5 mm instead of 3 mm.

There is a positive association between total IgE and skin test results. Thus, determination of total serum IgE is a useful indicative of the presence of an IgE-mediated allergy. High values of total IgE are notable in the 10-15 years age group. Burrows et al. (1) found that allergic rhinitis was associated primarily with skin test reactions, independently of the total IgE level, whereas asthma was closely related to the total IgE level.

Concerning the hematological parameters, only the number of leucocytes and eosinophils yield additional information. In this study a blood-eosinophilia is never found in combination with a negative skin test, not even in children. With a questionable or positive skin

test, eosinophilia is found in 17.0%. An elevated number of blood eosinophils is more frequently seen at an early age; in the 0-9 years age group 41.7% have an eosinophilia, this percentage decreases to 9.0% for the group of 9 years and older. Patients with a questionable or negative skin test more frequently have a leucocytosis than patients with a positive skin test; it seems that infection factors are contributing to the respiratory complaints in the first group.

A high eosinophil count in nasal smear is most frequently found in patients with a positive limited number of skin tests, least frequently in patients with a negative skin test. Nasal smear cytology with many eosinophils appears to support the diagnosis of IgE-mediated allergy, even in those patients with a so-called subclinical allergy (9, 15).

We also compared the results of the limited number of skin tests with the results of routine X-sinus (normal = clear sinus, or abnormal = partial or complete blockage). A total of 247 patients were studied in this way. No association was found between the results of the combined skin test and the findings on the X-sinus ($P = 0.61$, χ^2 test).

No significant relation was found between lung function (normal or abnormal) and the results of the combined skin test, the number of blood eosinophils, total IgE and the number of eosinophils in nasal smear. This appears to agree with the data that patients with positive skin tests do not suffer more frequently from non-specific lung disease (CNSLD) than patients with negative skin tests (8).

On the basis of these results it can be concluded that screening for the presence of an IgE-mediated allergy in people with upper respiratory tract complaints can be done with a limited number of skin tests (rye grass, timothy, birch, house dust mite and cat). If indicated, the screening can be supplemented by an extended series of skin tests, measurement of total IgE and specific IgE (RAST) and measurement of the number of eosinophilic granulocytes in nasal smear and blood. It must be emphasized that these conclusions can be drawn for an ENT practice only. For individual cases or for other groups of patients, extended skin tests might be

indicated. The Commission Standardization Skin test of the Dutch Society of Allergy advises a first diagnostic orientation with 15-30 skin tests for persons of 12 years and older; for children upto 12 years a first orientation with 10 tests is advised (5).

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