

Evaluation of Laboratory Tests in Childhood Allergy

Total Serum IgE, Blood Eosinophilia and Eosinophil and Mast Cells in Nasal Mucosa of 178 Children Aged 3 Years

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The diagnosis of atopic disease is often difficult in small children because of differences in symptoms and lack of specific and reliable laboratory tests. We evaluated the significance of four commonly used laboratory tests – blood eosinophil count, total serum IgE, and eosinophil and mast cells in the nasal smear – as indicators of atopy in 178 children aged 3 years. The children were followed from birth and examined at the age of 3 years. Symptoms of immediate hypersensitivity including atopic dermatitis, food allergy and pollen or animal allergy were recorded. Severe or obvious atopy correlated with the highest levels of serum IgE. A total serum IgE level higher than 150 U/ml was found to be strongly suggestive of atopic disease. A blood eosinophil count higher than $600 \times 10^9/l$ as well as an increased number of eosinophil and mast cells in the nasal smear were associated with atopy. On the other hand, normal levels of these laboratory tests did not exclude atopic disease. In other words, all of the tests were high in specificity, but low in sensitivity. Consequently, when small children's atopic disease is being diagnosed, emphasis can be laid on the elevated levels of serum total IgE, blood eosinophil count and eosinophil and mast cells in the nasal smear, all of which separately, but especially together, give valuable information on atopy.

Key words: atopy, diagnosis; eosinophilia in blood; eosinophils; IgE, total; mast cells; nasal smear.

Accepted for publication 26 January 1981

CLINICAL ASPECTS

The significances of serum total IgE, eosinophilia in blood, and the eosinophil and mast cells nasal mucosal smear were evaluated as diagnostic criteria of atopic disease. The children were followed up from birth to 3 years of age, and atopic dermatitis, food allergy, and pollen or animal allergy were recorded as symptoms of atopy. A total serum IgE higher than 150 U/ml, a blood eosinophilia higher than $600 \times 10^9/l$, as well as an increased number of eosinophil or mast cells in the nasal mucosal smear were all separately associated with atopic disease. The specificity of all of these tests was high, which means that "false positive" results were rare. On the other hand, the sensitivity was low. Normal levels in these laboratory tests did not exclude atopic disease.

The diagnosis of atopic disease may sometimes be quite difficult. This concerns small children in particular, when the skin tests are not yet reliable (1, 17). Atopic respiratory disease, when severe, and atopic dermatitis, when typical, can be diagnosed on the basis of the clinical

picture. However, symptoms of food allergy or allergic respiratory symptoms in small children are often vague and can easily be missed. Attention and expectations are directed to several laboratory tests as an aid in reaching the diagnosis.

Eosinophilia in blood is a common feature of several types of hypersensitivity reactions (15). In addition to allergic airway diseases and atopic dermatitis, blood eosinophilia occurs in some other conditions (15). An increased number of eosinophils is more frequently associated with hay fever and asthma than with atopic dermatitis or drug hypersensitivity. Eosinophilia in blood occurs during active phases of atopic disease (19, 20). In adults, several studies have proved that blood eosinophilia seems to be of little diagnostic value in the evaluation of nasal allergy (16, 20). In children, however, blood eosinophilia might occur more frequently than in adults.

High levels of serum total IgE are most commonly associated with atopic disease and, in addition, with parasitic infestations (3, 10). However, IgE levels show a wide distribution both in health and in atopic disease. Children who have food intolerance or respiratory allergy in addition to eczema are reported to have higher serum IgE levels than those with "pure" atopic dermatitis (6, 9, 23, 24). Normally, the serum IgE concentration increases slowly during childhood (12) and, moreover, an increase is registered after exposure to the allergen to which the patient is hypersensitive. In the first year of life even a slightly elevated IgE value may indicate an atopic predisposition (4, 14). A level of total serum IgE more than + 2 s.d. over the age-specific mean should suggest actual or threatening atopic disease (13).

Both the eosinophil and the mast cell counts in the nasal smear have been shown to correlate particularly with inhalant or food allergy (2, 5, 18, 22). Both types of cells increase in number after challenge with inhalant or food antigen and during the pollen season (18). On the other hand, a clear decrease in the nasal mast cells has been observed during elimination diet in food allergy (22). Eosinophils in the nasal smear were a sign of active nasal allergy in an epidemiological study on students and children. A correlation between increased number of mast cells and allergic rhinitis was only revealed in students, not in children (16).

The purpose of the present study was to find out whether laboratory tests would be helpful in

classifying small children as atopic and non-atopic, or in determining the type of possible allergy. Special interest was paid to the concentration of serum total IgE, blood eosinophil count and number of mast cells and eosinophils in the nasal smear in reference to their correlation with clinical atopic symptoms and with each other.

SUBJECTS AND METHODS

We evaluated atopic symptoms and signs in a group of 178 children at the age of 3 years. The initial series consisted of 256 randomly selected healthy newborn infants, who were closely followed up during the first year of life (21). Solid foods were introduced similarly to all infants; cooked vegetables and fruit at 3.5 months, cereals at 5 months, meat and eggs at 6 months, dairy products at 8 months, and a normal mixed diet at 9 months (21). Fish and citrus fruits were avoided up to 1 year of age. Breast feeding was recommended at first for every infant and was the exclusive source of milk in 24% up to 6 months of age. At weaning, either a commercial infant formula or a home-prepared cow milk formula was started (21). After 1 year of age the diet was free.

Out of the 256, 237 completed the first-year follow-up, and 178 could be reached for re-examination at 3 years of age.

Atopic symptoms and signs were recorded and samples for laboratory tests were taken by one of the authors (M.K.).

Definition of atopic symptoms and signs

Family history of immediate hypersensitivity was defined as the occurrence of allergic asthma, allergic rhinitis, atopic dermatitis or food allergy in at least one parent or sibling. Symptoms and signs of immediate hypersensitivity in the children included atopic dermatitis, food allergy causing heavy vomiting or skin rash after challenge at home, and pollen or animal allergy defined as history of wheezing after exposure. The severity of atopic symptoms was graded into three categories: grade 0, no

atopy; grade 1, suspected atopy; and grade 2, severe or obvious atopy (21).

Laboratory determinations

Venous blood was drawn for the eosinophil count in the forenoon, and a count equal to or higher than $600 \times 10^9/l$ was defined as eosinophilia and $400\text{--}600 \times 10^9/l$ as intermediate level. Serum total IgE was determined with the Phadebas IgE PRIST kit (Pharmacia Diagnostics, Uppsala, Sweden). A nasal smear was taken by wiping the mucosa with a cotton-tipped applicator. The sample was rolled onto a glass slide, fixed by air-drying and stained by the eosin, Wright's and Papanicolaou's techniques. (Eosin methylene blue staining demonstrates the eosinophil cells, and the basophil cells are best visualized by Wright's stain). The cells were counted microscopically. The performer of the microscopy did not know of the presence of allergy. A mast cell count higher than 20 per slide was defined as increased. The eosinophilia was graded semiquantitatively as $-$, $+$, $++$ or $+++$ by the criteria of Hansel (7).

Statistical methods

Chi-square test and Student's *t* test were used in the statistical analyses. Logarithms were used in the calculations of the IgE values.

RESULTS

Eosinophilia in blood was found to correlate with atopic symptoms and signs. Blood eosinophilia higher than $600 \times 10^9/l$ was found in six children (3%) out of 177, four (67%) of whom had atopic disease compared with 25% of those with eosinophil counts below $400 \times 10^9/l$ ($P < 0.05$) (Table 1). The correlation was strongest in inhalant allergy. (Table 1).

Eosinophilia in the nasal mucosal smear was found in 11 children, seven (64%) of whom had atopic disease. Only 25% of children without nasal eosinophilia were considered atopic ($P < 0.01$) (Table 2). Again, the best correlation was found in inhalant allergy.

Only three of the 177 children had more than 20 mast cells per slide in the nasal mucosa. All of them had atopic disease: one had atopic dermatitis, two had pollen or animal allergy and all three had food allergy (Table 2). Of those with only a few or no mast cells, only 26% had atopic disease ($P < 0.005$) (Table 2).

Eosinophilia in blood correlated strongly with eosinophilia in nasal mucosa ($P < 0.001$), whereas no correlation was found between the nasal eosinophils and mast cells (Table 3).

Serum total IgE was determined in 169 children, who were graded arbitrarily into groups with total IgE < 70 , $70\text{--}150$, and > 150 U/ml. The prevalence of atopic disease in these groups was 26%, 31% and 67%, respectively (Table 1).

Table 1

Occurrence of atopic disease and the correlation with eosinophilia in blood and total serum IgE

Eosinophilia in blood	<i>n</i>	Atopic disease	Atopic dermatitis	Food allergy	Pollen or animal allergy
a) $> 600 \times 10^9/l$	6	4 67%	2 33%	3 50%	3 50%
b) $400\text{--}600$	13	6 46%	2 15%	5 39%	1 8%*
c) < 400	158	39 25%*	16 10%	36 23%	3 2%**
IgE					
a) > 150 U/ml	6	4 67%	2 33%	4 67%	1 17%
b) $70\text{--}150$	16	5 31%	3 19%	5 31%	1 6%
c) < 70	147	38 26%*	13 9%*	33 22%*	5 3%

* $P < 0.05$ compared with group a.

** $P < 0.001$ compared with group a.

Table 2.

Occurrence of atopic disease and the correlation with eosinophils and mast cells in nasal mucosal smear

Eosinophilia in nasal mucosa	n	Atopic disease	Atopic dermatitis	Food allergy	Pollen or animal allergy
a) Positive	11	7 64%*	4 36%*	7 64%**	4 36%***
b) Negative	166	42 25%	16 10%	37 22%	3 2%
Mast cells in nasal mucosa					
a) > 20/slide	3	3 100%**	1 33%	3 100%**	2 67%***
b) 0-20/slide	174	46 26%	19 11%	41 24%	5 3%

* $P > 0.01$ compared with group b.** $P > 0.005$ compared with group b.*** $P > 0.001$ compared with group b.

Table 3.

Correlation of eosinophil cells in nasal mucosa with blood eosinophilia and with nasal mucosal mast cells

Eosophil cells in nasal mucosa	n	Eosinophilia in blood $>600 \times 10^9/l$ (n = 6)	Mast cells in nasal mucosa 0-20 (n = 174)	Mast cells in nasal mucosa > 20/slide (n = 3)
Positive	11	4 36%*	10 6%	1 33%
Negative	166	2 1%*	164 94%	2 67%

* $P < 0.001$.

When correlated to the grade of atopy, the highest mean total serum IgE was found in children with severe or obvious atopy, whereas no difference was found between those with suspected and those with no atopy (Fig. 1). The level of serum total IgE also correlated with the other laboratory tests. Children with blood eosinophilia exceeding $600 \times 10^9/l$ as well as those with nasal eosinophilia had a higher mean serum IgE than children without eosinophilia ($P < 0.025$ and $P < 0.001$, respectively) (Fig. 1). Regarding the nasal mast cells, the correlation with serum IgE did not attain statistical significance.

The characteristics of serum total IgE, blood eosinophilia, nasal mucosal eosinophilia and nasal mast cells as diagnostic tests in the evaluation of childhood allergy are shown in Table 4. The specificity of every test was high; on the other hand, the sensitivity was low.

DISCUSSION

Our data suggest that in the diagnosis of atopic disease in small children valuable information can be obtained by the usual laboratory tests, e.g. the blood eosinophil count, the eosinophils and mast cells in the nasal mucosal smear, and the serum total IgE. The definition of the specific type of atopy by means of laboratory tests is difficult since one child often suffers from several types of allergy.

Eosinophilia in blood and/or nasal smear was an indicator of atopic disease. Pollen or animal allergy seemed often to be the basis, although the information mostly was non-specific regarding the type of allergy. A false-positive blood eosinophilia is known to be due to parasitic infestation by e.g. *Ascaris* or *Oxyuris* in small children. On the other hand, a quiet

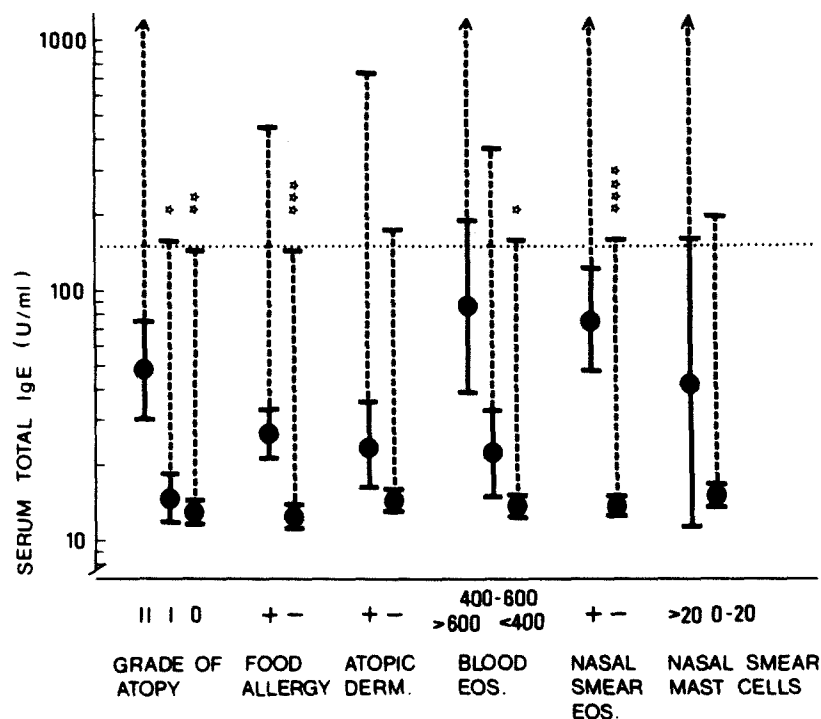


Fig. 1. Serum total IgE in groups of children with or without atopic symptoms, with high, intermediate or normal blood eosinophils, and with or without eosinophil or mast cells in the nasal smear. Solid circles and solid lines indicate the means $\pm$ s.e., and the dotted lines indicate $+ 2$ s.d. Asterisks indicate significant differences compared with the group on the left regarding the same finding. **** $P < 0.001$, *** $P < 0.005$, ** $P < 0.01$, and * $P < 0.025$.

Table 4.
Characteristics of serum total IgE, blood eosinophilia, eosinophilia in nasal mucosa, and mast cells in nasal mucosa in the evaluation of childhood allergy

	Serum total IgE > 150 U/ml	Eosinophilia in blood > 600 $\times 10^9/l$	Eosinophilia in nasal mucosa	Mast cells in nasal mucosa > 20/slide
Predictive value ¹	67 %	67 %	64 %	100 %
Sensitivity ²	9 %	8 %	14 %	6 %
Specificity ³	98 %	98 %	97 %	100 %
Validity ⁴	73 %	73 %	74 %	74 %

¹ Percentage of right positive results out of the positive.
² Percentage of atopics verified by the test out of the atopics.
³ Percentage of healthy subjects verified by the test out of the healthy.
⁴ Percentage of right results out of total.

period outside the season and without chal-
lenge with antigens might explain the low
eosinophil counts seen in the atopic children.
Upper airway infections may also affect the
number of eosinophils and perhaps also of
mast cells in the nasal smear (8, 16). Mast cells
in the nasal mucosa have been suggested to
correlate with food allergy (5, 22) although
there are also controversial reports (11). In the

present study only three children had a high
number of mast cells and all of them had food
allergy. However, these three were only a small
proportion of the food allergists. On the other
hand, high numbers of nasal mast cells are
known to be associated with food provocation,
with a peak approximately 25 h after the chal-
lenge. This peak disappears within a relatively
short time and can easily be missed (22). Our

children had no preceding provocation test, which may explain the absence of mast cells also in the food-allergic subjects. The study of nasal mast cells after food-antigen provocation might therefore be more useful.

The present study also evaluated the role of total serum IgE as an indicator of atopic disease. As seen in Fig. 1, the upper limit of "normal", as defined by + 2 s.d. above the mean, was approx. 150 U/ml for children without symptoms of atopy, for children with blood eosinophils below $400 \times 10^9/l$, and for children with no eosinophils or less than 20 mast cells in the nasal smear. Accordingly, a serum total IgE level of about 150 U/ml can be regarded as the upper limit of normal in children aged 3 years, and values above that limit as suggestive of atopic disease. The lower limit of normal, on the other hand, can hardly be settled on the basis of this data. Even some children with obvious or severe atopic disease had quite low IgE values, as had those with a high blood eosinophil count or those with eosinophils or mast cells in nasal mucosa. There is no "safe" lower limit of serum total IgE.

In summary, we conclude that a serum total IgE higher than 150 U/ml, a blood eosinophilia higher than $600 \times 10^9/l$, and an increased number of eosinophils or mast cells in nasal mucosal smear, are all suggestive of atopic disease in young children. All of these tests are high in specificity, but low in sensitivity. Normal values of these parameters do not exclude atopic disease.

ACKNOWLEDGEMENTS

This study was supported by grants from the Foundation for Pediatric Research, Finland, and the Foundation for Allergologic Research, Finland.

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