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ATOPIC ALLERGY AND SERUM IgE IN RANDOMLY SELECTED EIGHT-YEAR-OLD CHILDREN

By

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Atopy has been defined as a tendency to produce specific antibodies of immunoglobulin class E (IgE) as the result of repeated exposition to common environmental antigens (25). It has been possible to analyse serum concentrations of IgE for the last 10 years (13, 14, 27). In healthy newborns the serum IgE level is below 1 kU/l (1 kU is equivalent to about 2.4 µg) and its concentration increases slowly during childhood to reach a maximum in children 10-14 years of age (18). A rather rapid decrease is found after puberty (9).

Atopic diseases—atopic dermatitis, allergic rhinitis, bronchial asthma and certain forms of urticaria—are, apart from parasitic infestation, the most common causes of high IgE levels (15). However, IgE levels show a great dispersion in health as well as in atopic disease.

Hence, there have been difficulties in discriminating between atopic and non-atopic individuals and in interpreting isolated IgE values (12). After having established a highly selected reference material of non-atopic children from 0 to 15 years of age (21) we were able to evaluate the new reference limits on a randomly selected group of 8-year-old schoolchildren living in the same region as the reference children. The aims of the study were:

- a) to compare two different radioimmunoassay techniques

for the determination of serum IgE levels in a non-selected group of children,

b) to evaluate the clinical significance of serum IgE and RAST in relation to family and individual histories, and

c) to find out if high IgE levels could predict atopic disease during the first 2 years after blood sampling in this age group as has been shown previously in younger infants and children (11, 21).

MATERIAL AND METHODS

A sample of 212 children was selected at random from among the 1483 8-year-old school children in the community of Linköping, Sweden, in 1973. Case histories were collected using a questionnaire with main emphasis on the occurrence of allergic disease and infections in the children as well as in their family members (parents and siblings). Answers were received from 210 of the children. Among these, 164 assented to blood sampling which in all cases was performed with the consent of their parents. All samples were taken in November to minimize the effect of possible seasonal allergy in the children. Serum was separated and frozen at -20°C . When all samples had been collected they were simultaneously analysed. Case histories were evaluated without knowledge of the IgE results.

Serum IgE was analysed using two different radioimmunoassays: Phadebas® IgE (radioimmunosorbent) test (RIST), an inhibition radioimmunoassay with Sephadex coupled anti-IgE (27), and Phadebas IgE PRIST®, a direct sandwich technique using paper discs as the solid phase. The PRIST technique was described by Cesca & Lundquist in 1972 (5) and evaluated recently (17). The results were expressed in kU/l and compared with those in a selected group of healthy non-atopic children (21).

A screening for specific reaginic antibodies was performed using the radio-allergosorbent test, Phadebas RAST®, in all 28 sera with a total IgE level above the geometrical mean $+ 2$ standard deviations (s.d.) for age using RIST, and in a further 28 children selected at random among those with lower IgE levels. The test was performed in accordance with the recommendations of the manufacturer. The following five allergens were used in the RAST: horse and cat dander, dust (Greer Incorp.), birch pollen and timothy pollen.

About 2 years after the blood sampling a new questionnaire was sent to all the families to find out the occurrence of possible allergic symptoms in the children and/or the family members. The parents were asked to describe the symptoms and to give the time of their onset in relation to the blood sampling. Furthermore, all possible information was collected from clinical records, whenever available, at the Department of Pediatrics, Linköping University Hospital.

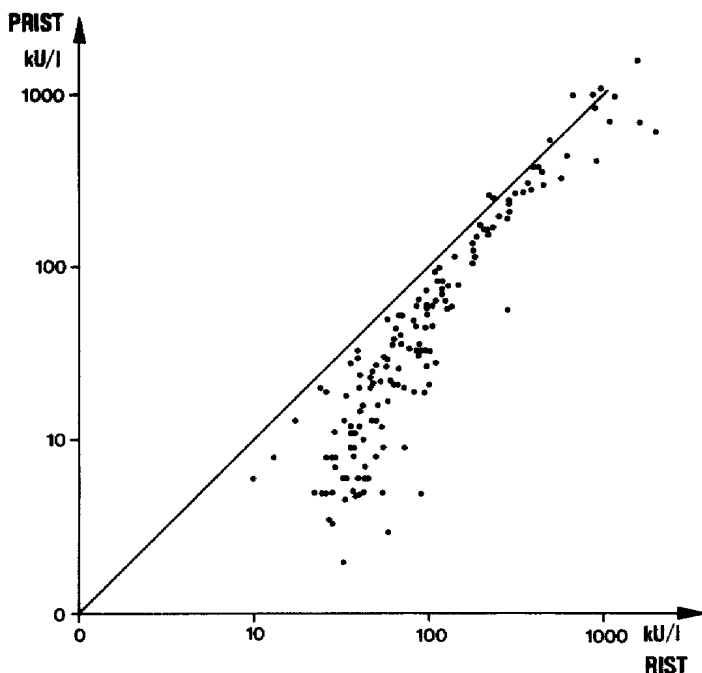


Fig. 1.

Comparison between IgE levels with the RIST and PRIST methods.

Obvious atopic disease was defined in the case of evident symptoms and/or signs of atopic disease: atopic dermatitis, allergic rhinitis, allergic urticaria and bronchial asthma.

Probable atopic disease was considered to be present when there was a history of any of the following symptoms not documented in previous medical records: itching flexural eczema, wheezing during three or more respiratory infections or on other occasions, a constant nasal discharge or sneezing and nasal itching without respiratory infections. Episodes of urticaria without known aetiology were also classified as expressions of a probable atopic disease.

Bronchial asthma and allergic rhinitis will be referred to as *respiratory allergies*, atopic dermatitis and urticaria as *skin allergies*. When diseases of both the respiratory and the skin types occurred in the same child the disease will be called *combined allergy*.

TABLE 1
IgE Levels in Relation to the Case Histories. Comparison between the RIST and PRIST Methods.

Method	IgE kU/l	n	Per cent	With atopic disease		Without atopic disease	
				Obvious	Probable	With FH	Without FH
RIST	<250	136	82.9	7	8	15	32
	>250	28	17.1	14	2	16	7
	Total	164	100.0	21	10	31	39
PRIST	<250	140	85.4	8	9	17	35
	>250	24	14.6	13	1	14	4
	Total	164	100.0	21	10	31	39
RIST	<250	121	82.9	7	8	15	32
	>250	12	17.1	14	2	16	7
	Total	133	100.0	21	10	31	39
PRIST	<250	123	85.4	8	9	17	35
	>250	10	14.6	13	1	14	4
	Total	133	100.0	21	10	31	39

FH = family history of atopic disease.

IgE levels were in this study regarded as *high* if they exceeded the $+ 2$ s.d. limit for age in healthy non-atopic children (18, 21), otherwise they were classified as normal.

RASTs were regarded as positive when the RAST score was 2-4, otherwise they were called negative.

RESULTS

The serum IgE levels showed a wide range from 1 kU/l to 1600 kU/l using PRIST and from 10 to 2000 kU/l using RIST. The results of these analyses are compared in Fig. 1. There is a good correlation between the two methods for IgE levels exceeding 50 kU/l. For lower levels RIST tends to give somewhat higher results than PRIST. At IgE levels above 250 kU/l, i.e. the $+ 2$ s.d. limit for age, using both methods, the differences are small. Using RIST, 28 children had IgE levels above this limit in comparison with 24 using PRIST (Table 1).

Fourteen of 21 (66.7 per cent) children with obvious atopic disease had high IgE levels using RIST. The corresponding incidence was 13/21 (61.9 per cent) using PRIST. No difference was found in the ability of the methods to discriminate between atopic and non-atopic individuals. Hence, the results of PRIST were used for the following presentation.

The case histories of the initial material (210 children), including the 164 who were submitted to IgE analyses, are presented in Table 2. The total incidences of obvious and probable atopic disease were 19.0 and 18.9 per cent, respectively. Thus, there was no significant difference in the incidence of atopic disease between the groups. Five children with bronchial asthma in the initial material who did not want to participate in the study were all known outpatients at the Department. Their IgE levels ranged from 28-17000 kU/l (RIST).

A family history of atopic disease was found in 11 out of 21 children with obvious atopic disease and in three out of 10 cases with probable atopic disease as compared with 38 out of 133 healthy children (Fig. 2). In all, 52 of the 164

TABLE 2
Case Histories. Comparison between the Initial Material and the Children in Whom IgE Was Determined.

Diagnosis	Initial material ($n = 210$)			IgE cases ($n = 164$)		
	Obvious	Probable	Total n Per cent	Obvious	Probable	Total n Per cent
Bronchial asthma	7	1	8 3.8	3	0	3 1.8
Allergic rhinitis	17	5	22 10.5	14	3	17 10.4
Atopic dermatitis	11	3	14 6.7	8	3	11 6.7
Urticaria	2	5	7 3.3	1	5	6 3.6
One atopic disease or more	27 (12.9)	13 (6.1)	40 19.0	21 (12.8)	10 (6.1)	31 18.9

Figures in brackets indicate percentage.

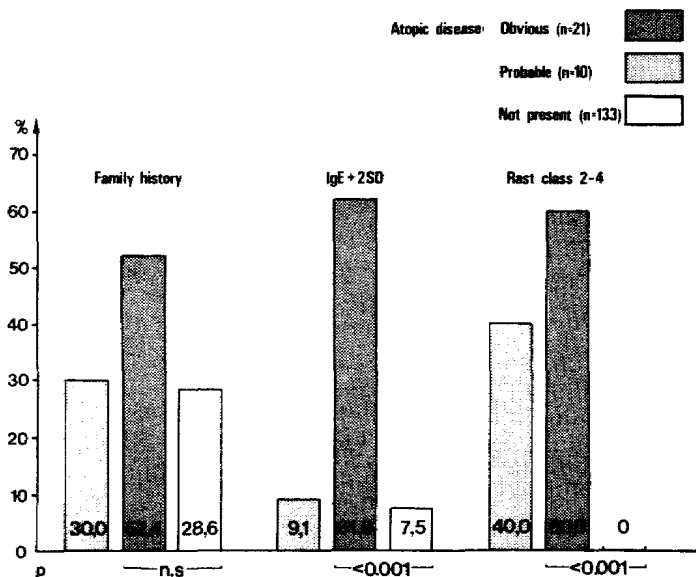


Fig. 2.

Comparison between the discriminative value of a positive family history of atopic disease, a high IgE level and a positive RAST screening in atopic disease.

children, i.e. 31.7 per cent, had a family history of atopic disease.

The IgE levels were significantly more often (χ^2 -test, $P < 0.001$) above the $+ 2$ s.d. limit for age in the children with atopic disease (14/31) than in those without (10/135) (Table 1). The distribution of logarithm-transformed IgE levels was found to be approximately Gaussian for healthy as well as for atopic children (Fig. 3) with an overlap between the curves. Twelve of the 13 children with obvious atopic disease who had high IgE levels had a respiratory type allergy, two of them combined with skin allergy. Only one of 11 children with probable atopic disease had a high IgE level.

A recent history of oxyuriasis was revealed in seven of the 164 children. All of them had normal IgE levels. There was

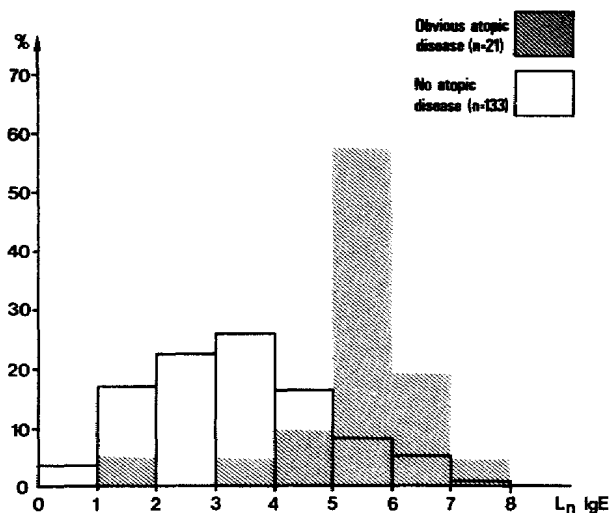


Fig. 3.

L_n IgE (PRIST) in the children with atopic disease and in those without.

no history of any other recent disease known to give high IgE levels (15).

The IgE levels are compared with the family and individual histories in Table 4. There was a higher incidence of atopic disease with higher IgE levels. Only one of our 21 children with obvious atopic disease had an IgE level below the geometrical mean for age. A family history of atopic disease was found in 34/123 (27.6 per cent) of the children with normal IgE levels as compared with 4/10 with higher levels; hence, no significant difference was found in this respect.

The results of RAST are presented in Table 5. Ten of the children with high IgE levels had positive RAST. Three of these children developed their symptoms of atopic disease after the blood sampling. There was no positive RAST in any child who was healthy during the whole observation period. Only one positive RAST was found in the randomly selected group of 28 children with IgE levels below the

TABLE 3
IgE Levels in Relation to Diagnosis.

Type of disease	<i>n</i>	Arithm. mean	Range	No. of samples > + 2 s.d.
<i>Obvious cases</i>				
Respiratory	12	453	21-1000	10
Skin	7	134	4.6-385	1
Combined	2	950	300-1600	2
Total	21	394	4.6-1600	13
<i>Probable cases</i>				
Respiratory	2	175	39-310	1
Skin	8	21.5	1-57	0
Total	10	52.2	1-310	1
TOTAL	31	284	1-1600	14

+ 2 s.d. limit. This positive test was found in a boy with a perennial rhinitis of probable atopic aetiology.

The incidence of positive RAST was 9/15 in the children with obvious atopic disease, 2/5 with probable and 0/36 without such disease (Fig. 2).

Twenty-four children had IgE levels above the + 2 s.d. limit (Table 4). In seven of these, the high level was explained by the presence at sampling of an actual atopic disease, one probable and six obvious cases. In all, 11 cases of obvious and six cases of probable atopic disease developed during the observation period. In seven of these, all of them obvious cases, the onset of disease was preceded by a high serum IgE level. The positive family history of atopic disease may possibly explain the high IgE levels in a further four of the children. In all, 18 of the 24 cases with high IgE levels may thus be explained, whilst six such cases, i.e. 3.7 per cent of the whole material, remain unexplained.

The distribution of the IgE levels in relation to the occurrence of atopy is compared with theoretical figures of incidence

TABLE 4
IgE Levels (PRIST) in Relation to the Diagnosis at the

IgE levels	Total		No atopic disease at either investigation			
	π	Per cent	Total π	Per cent	No FH	FH
< -2 s.d.	1	0.6	1	100.0	1	0
> -2 s.d. < -1 s.d.	12	7.3	11	91.7	9	2
> -1 s.d. $< \bar{Y}$	38	23.2	34	89.5	24	10
$> \bar{Y} < +1$ s.d.	62	37.8	54	87.1	39	15
$> +1$ s.d. $< +2$ s.d.	27	16.5	23	85.2	16	7
$> +2$ s.d.	24	14.5	10	41.7	6	4
Total	π	164	133		95	38
	Per cent	100.0	81.1		57.9	32.2

FH = family history of atopic disease.

$\bar{Y}$ = geometric mean.

s.d. = standard deviation.

calculated by Hamburger (11) in Table 6. Atopic disease is highly probable at IgE levels above 700 kU/l and rather improbable below 100 kU/l at this age, but no distinct discrimination is possible between atopy and non-atopy.

DISCUSSION

Serum IgE levels occur in minute concentrations in healthy children, but the range is very wide (Fig. 1), indeed much wider than for any other immunoglobulin. This necessitates a refined technology for serum IgE determinations. Most current methods include the use of radioactive IgE (inhibition methods) or anti-IgE (direct methods). Inhibition methods such as the original Phadebas IgE test tend to overestimate serum IgE levels in the lower range, i.e. below about 50 kU/l, because of the non-specific interference of serum proteins (3, 17). This may be overcome by the use of a correction factor in the calculations, but in newborns there is, even so, a tendency for the RIST to give higher IgE values

Initial Investigation and at the Follow-Up (2 Years Later).

Probable atopic disease			Obvious atopic disease		
Total	Initially	Follow-up	Total	Initially	Follow-up
0	0	0	0	0	0
1	0	1	0	0	0
3	1	2	1	1	0
5	2	3	3	1	2
0	0	0	4	2	2
1	1	0	13	6	7
10	4	6	21	10	11
6.1	2.4	3.7	12.8	6.1	6.7

than the direct sandwich radioimmunoassay PRIST in which paper discs are used as the solid phase (17).

Also in the present study the correspondence between the two methods was good for IgE levels above 50 kU/l. At lower levels the PRIST values tended to be lower than the RIST values. The PRIST, which also is more simple to perform (17), equalled the RIST in the ability to discriminate between atopic and non-atopic subjects. The PRIST is therefore recommended for IgE determinations in all ages of childhood as well as in adults (16).

One of the difficulties in allergy research is the lack of agreement as to which symptoms should be regarded as expressions of atopy. Perhaps there are no distinct differences between atopic and non-atopic, but rather degrees of "atopicness" (11). It seems justified to use the term "atopic" only for diseases in which IgE-mediated reactions have been proven to occur frequently. This is why the study was restricted to allergic rhinitis, bronchial asthma, atopic dermatitis and urticaria.

The total incidence of atopic disease as well as of the four diseases listed above was nearly identical in the initial material (19.0 per cent) and in the children in which IgE was

TABLE 5

Results of RAST in the 28 Children with High IgE Levels and the 28 Randomly Selected Controls.

RAST score	IgE level (RIST)	Atopic disease			Total
		Obvious	Probable	Not present	
0-1	> + 2 s.d.	5 (2)	0	13	18 (2)
	< + 2 s.d.	1	3	23	27
2-4	> + 2 s.d.	9 (5)	1	0	10 (5)
	< + 2 s.d.	0	1 (1)	0	1 (1)
Total	> + 2 s.d.	14 (7)	1	13	28 (7)
	< + 2 s.d.	1	4 (1)	23	28 (1)
Total		15 (7)	5 (1)	36	56 (8)

Figures in brackets indicate cases who developed symptoms of atopic disease during the observation time.

determined (18.9 per cent). As the initial group was selected at random among all 8-year-old children in the community the material may be regarded as a representative sample of 8-year-old children. The initial drop-out (2/212) was small and at the follow-up of the 164 IgE-investigated there was no drop-out at all.

The data in the medical records were in good agreement with the questionnaire data. It is of course difficult to obtain reliable information about former and present atopic symptoms through questionnaires, but even after a direct investigation it may be difficult to differentiate between atopy and non-atopy (20). Atopic symptoms are often misunderstood, especially if they occur in early childhood, and may also be forgotten. However, the total incidence of atopic disease which was found is in accordance with findings in other studies, such as in a larger group of seven-year-old children living in the same region (18), and in other reports from Europe and North America (1, 10, 26).

The incidence of obvious bronchial asthma, 3.3 per cent, is

TABLE 6. *The Incidence of Atopic Disease at Different IgE Levels. Comparison between Theoretical Incidences (11) and the Findings in the Present Study*

IgE level	Acc. to Hamburger (11)		n	Present study		
	Theoretical per cent in the population	Atopic per cent		Per cent in the material	Obvious atopy per cent	Probable atopy per cent
0-100	67	5	124	75.6	3.2	7.3
101-350	21	18	25	15.2	40.0	4.0
351-700	9	30	9	5.5	33.3	0
701-	3	100	6	3.7	66.7	0
Total	100	12.8	164	100.0	12.8	6.1

in accordance with findings by e.g. Williams & McNicols (28).

The incidence of a family history of atopic disease (31.7 per cent) was high but in accordance with other findings (2, 18). As a disposition for atopic disease and elevated IgE levels seems to have a common genetic background (23) the high incidence of IgE levels above the $+ 2$ s.d. level for age is not surprising ($24/164 = 14.6$ per cent). However, a positive family history of atopic disease was not found significantly more often among children with high IgE levels than among those with normal levels.

The distribution of the natural logarithms of IgE levels in children with obvious atopic disease (IgE from 4.6 to 1600 kU/l) and in non-atopic children (IgE from below 1 to 1100 kU/l) approximates the Gaussian distribution (Fig. 3) with a significant shift to the right of the IgE maximum of the atopic group as has also been reported by Grundbacher (9) among others. It was impossible to detect a distinct discriminating IgE as could be expected from many other studies (15).

Hamburger (11) has made an attempt to evaluate the significance of a single IgE value by calculating the theoretical distribution of IgE values at different levels as shown in Table 6. Such a procedure may prove of some value for the clinician. However, the theoretical incidences were calculated for IgE in adults. As there is a peak of IgE levels in children from 10 to 14 years of age (18), figures of incidences at different numerical IgE levels will differ between age groups during childhood. Account should also be taken of the changing incidence of the four atopic diseases at different ages during childhood, the first disease to occur being atopic dermatitis followed by bronchial asthma, and from about 5 years of age, allergic rhinitis (4). Thus accordingly, eight of 11 cases of atopic disease which developed during the observation period were allergic rhinitis. After puberty there is a decrease in the incidence of new cases of atopic disease.

Another approach to the problem was made by Marsh et al.

(22) who calculated a "cut-off" limit which was defined as the IgE level at which the combined percentage of healthy individuals with high IgE levels and atopic individuals with normal IgE levels was minimized. The cut-off limit as calculated for the present material was 149/ kU/l. This limit was exceeded by 36 (22.0 per cent) of the children. Seventeen out of 21 children with obvious atopic disease had IgE levels above the cut-off limit. Such a cut-off limit, if calculated for each age group, might be of value in future screening programmes. However, all such calculations based on numerical IgE values would have to be established for all ages during childhood before they could be useful to the pediatrician. For clinical use, the *geometrical mean* seems of interest as in this material only one case of obvious atopic disease (a very mild case of atopic dermatitis) had an IgE level below this limit. This finding is in agreement with that stated by others (16).

The $+ 2$ s.d. level is also of interest as such a level is frequently used as the upper reference limit. Thirteen of the 21 children with obvious atopic disease had an IgE level above this limit, but at the time of sampling the diagnosis was established in only six of these, and in one child with probable atopic disease. Six of the remaining 17 cases with high IgE levels, i.e. 35.3 per cent, were explained later on by the development of atopic disease. Probably, in an extended study, an even larger number of the children with high IgE levels will develop atopic disease in the near future, predominantly those with a family history of atopic disease (18). It has been shown by Chambers & Glaser (6) that positive skin tests may often be found before the onset of clinical hay fever, especially during childhood. More recently, Foucard (7, 8) demonstrated the presence of positive RAST and high IgE levels in children with "asthmatoïd bronchitis" but before evident symptoms of atopic allergy. Also studies by the Hamburger group (24) and by our group (18, 19, 20) have revealed that atopic symptoms in infants and children are often preceded by high serum IgE levels. In our experi-

ence of 439 children who were followed-up 18–24 months after sampling, 30 out of 44 (68.2 per cent) children who developed obvious atopic disease during the observation period had high IgE levels before the onset of symptoms. An IgE screening in high risk groups should enable prophylactic measures to be taken already in the preallergic state.

RAST, here used as a screening, was significantly more often positive in children with obvious atopic disease (Fig. 3) than in the remainder. A comparison was made between the discriminating value of a family history (taken by questionnaire), an IgE test (with PRIST) and the RAST screening (five allergens), and the result is in definite favour of the immunochemical diagnosis. Thus, with an equivocal case history, an IgE determination (with PRIST), preferably combined with a RAST screening (with allergens adapted to the age of the client) is of definite value for the discrimination between atopy and non-atopy.

SUMMARY

The incidence of atopic allergy and serum IgE levels as well as specific IgE antibodies was studied in a randomly selected sample of 164 8-year-old children who were followed-up for 2 years. The total incidence of atopic disease was 18.9 per cent. Serum IgE levels were above $+ 2$ s.d. for the age before the onset of atopic disease in seven of 11 children who developed an atopic disease during the observation period. The direct paper disc sandwich radioimmunoassay, PRIST®, equalled the Phadebas® IgE test for discriminating between atopy and non-atopy, but PRIST is preferred because of its simplicity. Actual or future atopic disease is most probable when the serum IgE is above the $+ 2$ s.d. limit for age. Serum IgE levels below the geometrical mean for age are rarely found in atopic disease. An IgE determination with PRIST will give more discriminative information than the family history and is recommended for routine purposes when there is a history of possible atopic allergy in a child.

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