

Atopic Allergy and Serum IgE Concentrations in Randomly Selected Children Followed Up from 8 to 12 Years of Age

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A total of 159 children selected at random were followed up from the age of 8 to 12 years regarding the development and cumulated incidence of atopic disease as well as serum IgE concentrations. The cumulated incidence, including healed cases, rose to 25.8%. The highest prevalence was found for allergic rhinitis (12.2%). Serum IgE concentrations decreased significantly in both healthy and atopic subjects, and indicated a peak in total IgE concentration in early school age. The allergy predictive value of elevated IgE concentrations was confirmed. Low concentrations of allergen-specific IgE were found in 14.1% of children healthy before and during the observation period, indicating that transient production of IgE antibodies is a normal phenomenon. Finally, the stability of IgE was excellent during the first 2 years at -20°C but later on concentrations tended to decrease, especially in the lower range.

Key words: allergy; children; IgE; stability

Accepted for publication 1 February 1984

CLINICAL ASPECTS

Healed and active atopic disease was common in 159 children selected at random and followed up from 8 to 12 years of age. Although higher serum concentrations were found in children with atopic disease no complete discrimination was possible between atopic and non-atopic subjects using serum IgE determinations. However, active atopic disease was rare with IgE concentrations below the geometrical mean concentration. The allergy predictive value of a high serum IgE concentration in a previously healthy child was high. A positive RAST test against common inhalant allergens was rather often found also in healthy children. However, when a higher concentration of pollen-specific IgE was found in a healthy child, atopic symptoms tended to develop during forthcoming seasons.

Finally, some doubt was cast on the long-term stability of serum IgE at -20°C , especially at low concentrations.

Atopic diseases are common during childhood, and compared with healthy subjects, children suffering from these diseases usually show elevated serum IgE concentrations. Serum IgE concentrations in infants and children slowly increase to a peak during school age (3, 6, 11, 14). The range of IgE concentrations in healthy school children is wide and the distribution is almost gaussian when log values are used (12). The development of atopic disease is sometimes preceded by a high serum IgE con-

centration (8, 13). Follow-up studies are thus needed when establishing reference material for serum IgE, so as to exclude subjects with present as well as subsequently developing atopic disease.

Specific IgE antibodies in serum are supposed to indicate that sensitization has taken place and to support a clinical diagnosis of atopic allergy. However, low titers of food antibodies have been demonstrated in the absence of atopic disease (4) and it seemed of interest to

study the occurrence of IgE antibodies against inhalant allergens in a randomly selected group of school children.

Furthermore, the aims of the present study were to evaluate, in randomly selected children followed up from 8 to 12 years of age, the prevalence and cumulated incidence of atopic disease in relation to the IgE concentration at age 8 and 12 years, to compare the change in IgE concentrations in these children and in children remaining free from atopic disease to age 12 years, and finally, to evaluate the stability of IgE at -20°C .

MATERIAL AND METHODS

From an original sample of 212 children, selected at random from all 1483 8-year-old school children in Linköping, 164 were available for blood sampling (mean age 8.3 years) in November 1973. A case history was taken by postal inquiry regarding family and personal history of atopic disease, and the results of this part of the study have been published (12).

It was possible to follow up 159 of these children (group A). Case histories and a second blood sample were taken at age 10 years. Samples of serum from 32 healthy non-atopic children (group H) were selected from group A for this study. When the children had reached 12 years of age case histories were taken by questionnaire, and available medical records scrutinized. A cumulated clinical diagnosis regarding active and healed atopic signs and symptoms was established, as defined below, in all 159 children. Blood samples were obtained from 134 of the children (group B) at a mean age of 12.6 years. Group B and group A had an equal history of atopic disease.

Atopic disease was described as obvious or probable, active or healed.

Obvious atopic disease was used only for repeated and typical signs and symptoms of atopic disease: atopic dermatitis, allergic rhinitis, bronchial asthma and allergic urticaria. In most cases the diagnosis was verified in the medical records.

Probable atopic disease was used when there was a history of signs and symptoms, not veri-

fied by medical records, of itching flexural eczema, wheezing during three or more episodes of respiratory infections, a constant nasal discharge or sneezing attacks and nasal itching. Episodes of urticaria of unknown etiology were also classified as probable atopic disease.

Serum was separated within 2 h and kept at -20°C pending analysis. Serum IgE was determined in duplicate using Phadebas IgE PRIST according to the instructions of the manufacturer. Specific antibodies of the IgE class were determined at age 12 years with Phadebas RAST using birch, timothy and mugwort pollen, horse dander, *Cladosporium* and house dust (Greer).

In 33 of 35 children from group B with a clinical diagnosis of obvious or probable atopic disease before age 12 years, a comparison was made between IgE concentrations found following storage for 2 years at -20°C and in the same sample 5.6 years after the sampling, i.e. 3.6 years later. No thawing was done except for these determinations. Similarly, serum samples in group H were analysed within a month and 2 years later.

Statistical methods applied were the Student's *t*-test, the sign test and the χ^2 test. Calculations on IgE concentrations including comparisons were made on log values to compensate for their skewed distribution (3, 11, 12). Accordingly, antilogs of the mean (geometrical mean) and of the mean ± 2 SD are presented.

RESULTS

The cumulated incidence of obvious atopic disease in group A increased during the observation period from 5.7 to 17.6% (Fig. 1). Including probable atopic disease, 25.8% of the children had a diagnosis of atopic disease before age 12 years. The change in prevalence by age was greatest for allergic rhinitis (Fig. 2). The cumulated incidence at age 12 years was also highest for allergic rhinitis (13.2%, Fig. 3).

An immediate family history of atopic disease was found in 48 of the 159 children (30.2%). The incidence was 46.4% for obvious atopic disease, 30.8% for probable atopic disease and

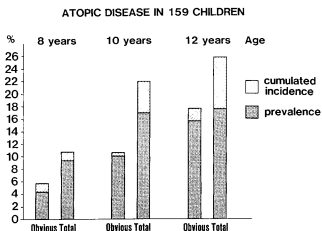


Fig. 1. Cumulated incidence, including healed cases, and prevalence of atopic disease from 8 to 12 years of age. Total includes probable atopic disease.

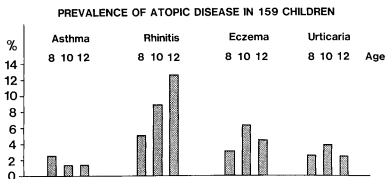


Fig. 2. Prevalence of atopic disease from 8 to 12 years.

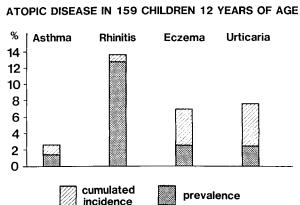


Fig. 3. Cumulated incidence (including healed cases) and prevalence of obvious and probable atopic disease at age 12 years.

Table 1
Cumulated diagnosis and IgE concentrations (kU/l) at 8 and 12 years

State of health	n	Age	Geometrical mean	+/- 2 SD	P
Healthy	99	8	25.9	1.3-508	<0.001
		12	13.3	0.9-169	
Probable atopic disease	10	8	31.4	0.7-1480	n.s.
		12	22.9	0.5-820	
Obvious atopic disease	25	8	96.7	9.7-2465	<0.05
		12	63.6	1.2-3498	
Total group	134	8	33.5	1.3-854	<0.001
		12	18.7	0.7-518	

Student's t-test was used for *P*-values.

26.3% for no atopic disease. Serum IgE concentrations decreased significantly ($P < 0.001$) with increasing age from 8 to 12 years both in group B (Table 1) and in the 32 healthy children constituting group H (Table 2). There was a non-significant trend towards lower IgE

concentrations in girls than in boys during the whole period. Children with obvious atopic disease showed a somewhat smaller decrease in IgE concentration than healthy subjects, but the decrease still appears significant ($P < 0.05$).

At age 12 years, IgE concentrations below the geometrical mean of the healthy group (13.3 kU/l) were found in one of 19 children classified as suffering from obvious *active* atopic disease and in 63 of the 99 children classified as healthy (Fig. 4). Concentrations above the geometrical mean +2 SD for the healthy group were rare without a history of atopic disease: such concentrations were found in two of 99 healthy children and in 10 of 19 cases with obvious *active* atopic disease.

In group H repeated IgE determinations on the same sample, which was kept frozen for 2 years, showed essentially the same results (Fig. 5). The geometrical means were 11.9 ($\pm$ SD: 1.0-134) and 12.8 (1.1-156) kU/l, respectively, and no significant difference was found by the Student's t-test nor by the sign test.

IgE concentrations as determined 5.6 years after the sampling in children with atopic disease showed a trend towards lower concentrations (Fig. 6) in comparison with results after 2 years at -20°C , but the difference was non-

Table 2
IgE concentrations in 32 healthy non-atopic children (group H) at 8, 10 and 12 years of age

Age (years)		Boys (n = 17)	Girls (n = 15)	Total (n = 32)
8	Geometrical mean	38.1	19.0	27.4
	$\pm$ 2 SD	3.5-410	0.5-610	1.4-545
	$\pm$ 1 SD			6.1-122
<i>P</i> (cp 8/12)		<0.05	<0.01	<0.001
10	Geometrical mean	27.6	14.4	20.6
	$\pm$ 2 SD	3.0-255	0.6-354	1.4-306
	$\pm$ 1 SD			5.4-79.5
<i>P</i> (cp 10/12)		<0.05	<0.01	<0.001
12	Geometrical mean	27.6	8.9	13.4
	$\pm$ 2 SD	2.2-140	2.2-147	1.1-155
	$\pm$ 1 SD			3.9-45.6

Student's t-test was used for *P*-values.

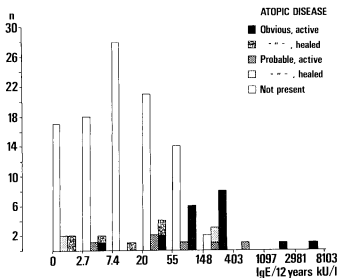


Fig. 4. IgE concentrations by diagnosis at age 12 years.

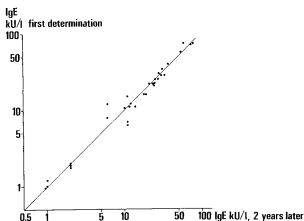


Fig. 5. Comparison of IgE concentrations in 32 healthy subjects determined with a 2-year interval. The sample was kept at -20°C between the determinations.

significant using t-test. However, as 26 of 33 concentrations decreased, a significant change was found using the sign test ($P < 0.01$). The geometrical mean concentration decreased from 80.4 to 61.8 kU/l (23.0%).

Serum IgE concentrations did not discriminate completely between atopic and non-atopic children at age 8 years (Fig. 7). Fifteen of 32 children with IgE concentrations exceeding 148

kU/l were classified as atopic in comparison with six out of 10 with IgE concentrations above 403 kU/l.

Atopic disease (obvious or probable) developed in 18 children during the observation period (Fig. 7). Allergic rhinitis developed in 13 children, healthy prior to the investigation at age 8 years. The serum IgE concentration was above the geometrical mean + 2 SD limit of

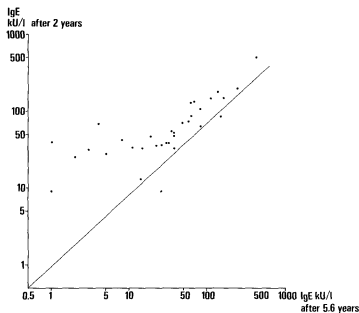


Fig. 6. IgE concentrations after 2 and 5.6 years in the freezer at -20°C in 33 children with atopic disease sampled at age 8 years.

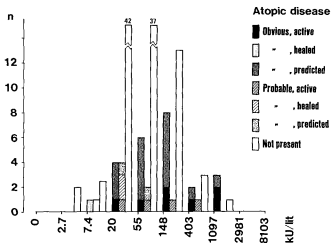


Fig. 7. IgE concentrations at age 8 years and diagnosis of atopic disease before age 12 years.

healthy subjects in nine of these 13 children and in all three children developing eczema. Thus, atopic disease was preceded by a high serum IgE concentration in 12 of 18 cases developing such disease during the observation period. A

positive RAST test was found prior to symptoms of allergic rhinitis in seven of the children also exhibiting a high total IgE concentration, but in none of the four other children with subsequent allergic rhinitis.

Table 3
Specific IgE antibodies at age 12 years, compared with the cumulated diagnosis

	No.	Positive RAST		Total No.	%
		Class 2 or more	Class 1		
Healthy	99	5*	9**	14	14.1
Atopic	35	16	5	21	60.0
Total	134	21	14	35	26.1

Atopic = probable and obvious atopic disease before 12 years of age.

* Grass pollen 3 (IgE 2.7, 47, 51) and house dust 2 children (IgE 5.7 and 15).

** Grass pollen 3, mugwort 1, birch pollen 1, horse dander 2 and house dust 2 children.

Specific IgE antibodies were found in 26.1% of the children at age 12 years (Table 3), significantly more often with atopic disease than with no atopic disease ($P < 0.001$ using the χ^2 -test). However, the incidence of a positive RAST test was 14.1% in the children with no suspicion of atopic disease during the observation period. Eight of the 14 positive tests were found using pollen as the allergen.

DISCUSSION

The cumulated incidence of atopic disease at age 12 years was somewhat higher than expected (9), but in accordance with findings in college students (1) and adolescents (7). Seventy of 281 (32%) subjects in the Finnish study, between 14 and 16 years of age, gave a history of past or present atopic disease. The prevalence of atopic disease in the present study was low at age 8 years but increased rapidly, mainly due to the development of allergic rhinitis which was found in 12% of the 12-year-old children. However, the prevalence as well as the incidence of bronchial asthma was biased by the fact that five children with well known bronchial asthma were among the initial sample of 212 children but did not want to take part in this study. Otherwise, no such bias was detected (12).

The development of atopic disease was preceded by a high serum IgE concentration in 12

out of 18 children. The predictive value of serum IgE determination in healthy subjects was thus confirmed (8, 13). Specific IgE antibodies were also found before atopic disease was overt in seven of 13 children developing allergic rhinitis, but only in children with high total IgE concentrations. Thus, the RAST analysis offers no advantages to the PRIST determination for predictive purposes.

Serum IgE concentrations decreased between 8 and 10 years of age in the children with no atopic disease. A further decrease was seen between 10 and 12 years of age. Similarly, children with past or present atopic disease showed lower IgE concentrations at age 12 as compared with 8 years of age, but the decrease was less pronounced as compared with that in healthy subjects. Apparently, the peak in IgE concentrations comes earlier than previously supposed (3, 6, 11) or at about 8 years of age in both healthy and atopic subjects. This may seem surprising as many children develop their symptoms of atopic disease after 8 years of age. However, IgE concentrations in serum are influenced by several environmental factors such as infections (2) and tobacco smoke (10) and are under the control of T-cells (5). The decreasing incidence of respiratory tract infections with age and the involution of lymphoid tissue such as adenoids during school age are well known. The underlying mechanism may be a maturation of T-suppressor cells. However, much remains to be elucidated regarding the process of immunological maturation.

As with other investigators we were unable to demonstrate significant differences in IgE concentrations between boys and girls. However, the present results in healthy subjects aged 8-10-12 years are suggested for use as reference material. At a comparable age (10 years) the present results show less dispersion than in our previous study (11).

Specific IgE antibodies against inhalant allergens are readily produced by atopic subjects but they were also found in 14% of healthy subjects aged 12 years. In nine of the 14 children the concentration was low (RAST class 1) but five children showed moderately high levels (RAST class 2). RAST determinations were also made at age 8 years in selected children, as reported previously (12): none of the 36 children with no atopic disease showed specific IgE antibodies of RAST class 2 or more at this age.

In this study IgE antibodies were found with low total IgE concentrations. This does not favour a theory that these children will probably develop atopic symptoms later on. The transient production of low or moderate concentrations of inhalant-allergen-specific IgE must be regarded as a natural phenomenon, as previously described for food antibodies (4).

Finally, the stability of IgE in a freezer at -20°C appeared excellent for at least 2 years. However, our results in serum samples stored for 5.6 years indicate that especially low concentrations tend to fall during this longer period. To my knowledge, no change has been made in the Phadebas IgE PRIST test kit during the study which could account for the present findings. However, the observation was made on a relatively small number of samples. Further studies seem advisable before using long-time-frozen serum samples, especially at low concentrations, for scientific purposes.

ACKNOWLEDGEMENTS

Financial support was received from Riksförbundet mot Allergi and from king Gustaf V 80 Year-Anniversary Fund. Excellent technical assistance was provided by Mrs. Lena Lindell, Mrs Margit Pettersson and Mrs Helene Nordahl.

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