

Serum levels of total IgE in non-allergic children

Influence of genetic and environmental factors

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The purpose of this study was to establish the range of total serum IgE in a healthy population lacking personal and family history of allergy, as well as the influence of genetic factors (family history of allergy), environmental factors (degree of air pollution), age, and sex on the serum IgE levels. Using a commercial enzyme immunoassay (Phadezym® IgE Prist) the mean serum level of IgE was determined in 363 non-atopic children from 0 to 12 years of age. The geometric mean of serum IgE increased according to age, indicating a positive correlation between both. Higher mean values of serum IgE were found for children with a family history of allergy, than for children without (27.82 and 14.49 U/ml respectively). The percentage of variation due to age was about 94.5% in children with no family history of allergy. The mean value of serum IgE increased with the degree of air pollution in the living area (15.49 U/ml in non-polluted areas, 20.78 U/ml in very polluted areas). However, the influence of air pollution was smaller than the influence of family history on the mean values of serum IgE. The mean value of serum IgE was not modified by sex.

Key words: air pollution; genetic factors; immunoglobulin E; family history of allergy.

Accepted for publication 4 December 1986

Since its discovery by Ishizaka et al. (9) and Johansson et al. (12), immunoglobulin E (IgE) has been the target of many studies designed to examine its biological role. The discovery of higher concentrations of serum IgE in allergic patients compared with non-allergic subjects (7, 20) was important, as it has enabled us to distinguish atopic from non-atopic disorders in an allergy diagnosis. More recent papers have shown high IgE values in other diseases, for instance parasitosis (17), certain types of tumors (11), immunodeficiencies (21) and dermatopathy (13).

Although many studies confirmed the existence of high IgE values in atopic disorders, a considerable overlap between the levels of total IgE in healthy subjects and allergic patients has also been shown (24).

The normal range of IgE in a healthy population has been defined by various authors (5, 17,

24), and the above-mentioned overlapping is explained by the heterogeneity in the groups of a normal population. This has led to a lack of accuracy in calculating the levels of IgE. IgE synthesis appears to depend on genetic factors, and preliminary observations have suggested that healthy subjects with a family history of allergy (FHA) could feature higher IgE levels than those without (2, 18). Subsequently, these findings were confirmed in an adult population (19). Moreover, other non-genetic factors, mainly environmental factors, could also have an influence on the serum IgE levels in a healthy population.

The aim of the present study is to establish the normal values of serum IgE in a non-allergic population from 0 to 12 years of age and to assess the influence of age, sex, FHA, and degree of air pollution in the living area.

Name: _____

Age: _____

Sex: _____

Home address: _____

1. Personal history of allergy

○ ○ ○ ○ ○

Asthma Rhinitis Ezcema Migraine Other

2. Extra-allergic pathology

○ ○

Helminthiasis Other

3. Immediate family history of allergy

○ ○

Asthma Other

4. Distant family history of allergy

○ ○

Asthma Other

5. Normal (negative, personal and family, history of allergy)

○

Fig. 1. Questionnaire used for selecting the population

MATERIAL AND METHODS

Population

To establish the normal range of IgE values, 363 children from 0 to 12 years of age were studied. They were chosen from patients at the emergency ward of the San Agustin Hospital, Aviles, when their blood was drawn for other analytical studies and if they met the following criteria: 1) no indications of allergic pathology, and 2) absence of extra-allergic pathology responsible for increasing the IgE values, principally, parasitosis, autoimmune disorders, and dermatopathies.

In the selection process, the children had to fill in a questionnaire (Fig. 1) with the following data: date of birth, home address, their present and past allergic history, and FHA among immediate (parents, sisters and brothers) and more distant (grandparents, aunts, uncles and cousins) relatives. The selected population was classified into five exclusive groups and placed in numerical order according to the data. In all cases verbal consent to carry out the study was obtained from the parents.

Living area

The population was divided into 11 small areas, using sedimentary material as an indicator of the amount of air pollution; this was achieved with the help of several counters distributed throughout the local area. A map was drawn to show the degree of pollution in the different areas according to the mean values of 1982. The border line of sedimentary material was 300 mg/m²/day, this value being the highest acceptable for healthy conditions, RD 833/75 (8). Areas under 300 mg/m²/day were considered non-polluted and those above polluted. In the second group, we differentiated between slightly polluted areas (mean levels between 300 and 600 mg/m²/day) and highly polluted areas (> 600 mg/m²/day).

IgE determinations

IgE assays were carried out in the serum, separated by centrifugation, from blood collected by venipuncture. The sera were stored at -20°C until the assays were carried out. No preservatives or additives were used.

The method used was a solid phase enzyme immunoassay based on the sandwich technique (Phadezym IgE PRIST, Pharmacia Diagnostica, Uppsala). The IgE values (U/ml) were obtained by taking the absorbance of the different samples and bringing them to the standard curve. The absorbance values from the IgE standards were plotted against the IgE concentration on lin-log paper, and then the IgE values were multiplied by the dilution factor. Each sample was run in duplicate and a serum with a known concentration of IgE was used as a control. The variation coefficient (CV) within-assay using Phadezym IgE Prist was 5.11 %. The same sample was run 25 times with a known IgE concentration in order to calculate the CV.

RESULTS

The sample characteristics are described in Table 1. The 363 children comprised 185 (50.98 %) males and 178 (49.02 %) females, the similar percentages thus avoiding the possibility of a sex difference. The statistical values for

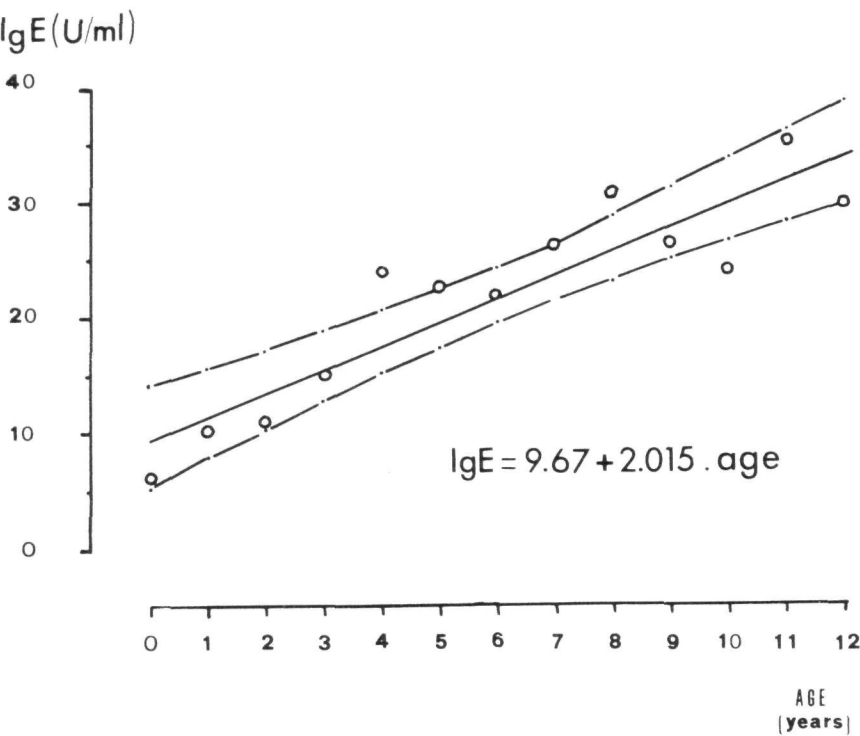


Fig. 2. IgE/Age regression line IgE/Age. Geometric IgE averages in relation to age.

each age group are described in the same table. For the study of IgE activity, a normal log distribution model was used.

IgE and age (total population)

To ascertain the relationship between the IgE mean values and age, a regression line was plotted using the data Age/IgE mean values

from Table 1. Fig. 2 shows the regression line of the mean IgE values and the regression lines which indicate the highest and lowest limit for a confidence percentage of approx. 95%. The equation of the regression line was:

$$\text{IgE (U/ml)} = 9.6779 + 2.0152 \times \text{age}$$

The regression line showed a variance of 81.8% (18.2% without explanation). Thus, the IgE variation values were explained by age; they increased in parallel to age, at least until the age of 12. A higher IgE mean value corresponded to an older age.

Table 1

Statistical IgE values from a non-allergic childhood population for each age group

Age (years)	M	F	IgE (U/ml)	Mean. log.	Variance
0	24	19	6.20	1.8251	0.6040
1	14	8	10.34	2.3362	1.2307
2	11	14	11.05	2.4020	1.0202
3	26	18	15.03	2.7100	1.0649
4	16	24	24.10	3.1824	1.0742
5	25	19	22.55	3.1156	1.5594
6	20	17	21.91	3.0869	1.4584
7	12	13	26.08	3.2613	1.9393
8	7	17	30.61	3.4212	1.0648
9	9	11	26.41	3.2736	1.4114
10	10	5	23.96	3.1764	1.2575
11	7	6	35.22	3.5616	1.3012
12	4	7	29.54	3.3859	1.4469

IgE and atopic family history

Table 2 shows the influence of FHA on the IgE values in a non-allergic childhood population; the geometric average was calculated in two different groups. The first was made up of 118 children (32.5%) with FHA and the other of 245 children (67.5%) without. The IgE mean value belonging to the first group was significantly higher than in the second one. Because of this, an attempt was made to distinguish between the closer and the more distant family, expecting to find a difference in the IgE mean values, but with no success, because there was not a significant difference between the two theoretical groups.

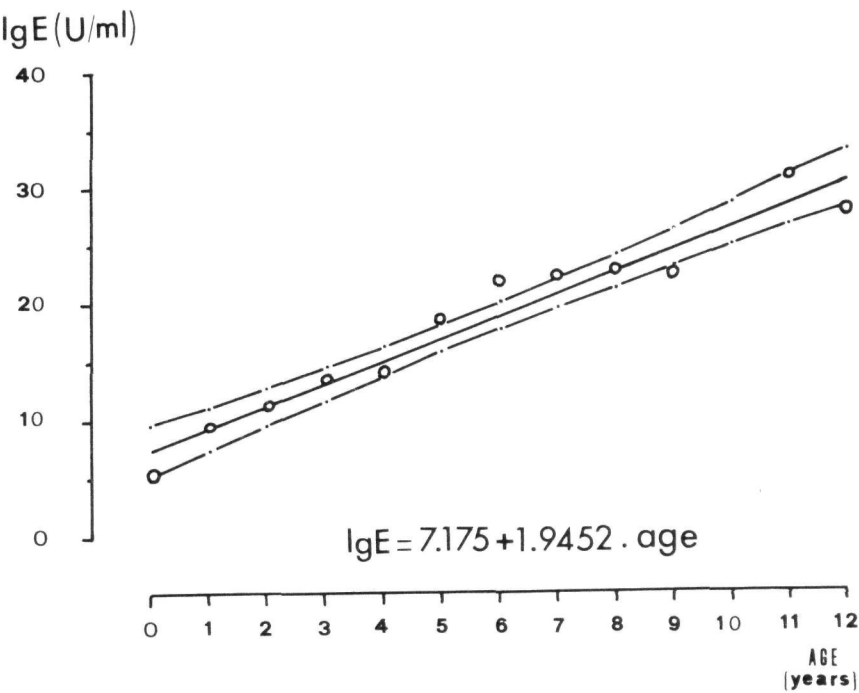


Fig. 3. IgE/Age regression line IgE/ Age. Geometric IgE averages considering only cases without atopic family history.

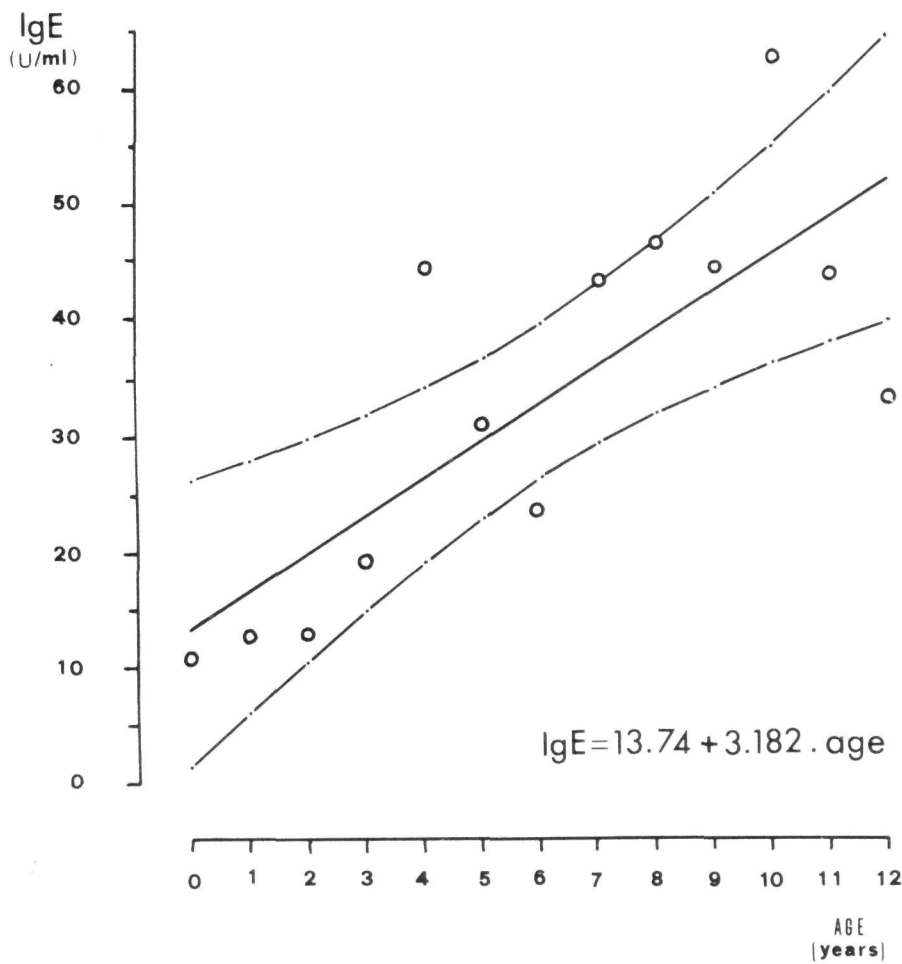


Fig. 4. IgE/Age regression lines IgE/ Age. Geometric IgE averages, considering the cases with atopic family history.

IgE and age (population with and without FHA)

Figs. 3 and 4 show the modification of the IgE mean values affected by FHA. Both figures

show the regression lines with a confidence of 95 % for the IgE values. It is clear that the best IgE/Age relationship was found in the group of children with no FHA, the results in the group

Table 2
Influence of family history on mean IgE values

	N	IgE	Mean log.	Variance	ts
Without FHA	245	14.19	2.6734	1.3304	5.0215
With FHA	118	27.82	3.3258	1.3906	(S)
Immediate FHA	65	25.34	3.2324	1.4620	1.2390
Distant FHA	53	32.93	3.4945	1.3245	(NS)

S = Significant; NS = Non-significant.

with FHA being a little more puzzling. Thus, the existence of FHA has an influence on the total IgE values in non-allergic children as shown by Figs. 3 and 4.

In the group without FHA, the effect of age on the IgE variation was 94.5%, while in the group with FHA this percentage decreased to 58.9%.

The IgE values in non-allergic children and in children without FHA were estimated using the substituted variables in the corresponding regression equation. Therefore, the IgE values in this group are a function of the age with very few variations (Table 3).

IgE and sex

Comparing the geometric mean of IgE between males and females shows that sex has no influence on the IgE values (Table 4).

Table 3
Estimated values of IgE (geometric mean and standard error) from non-allergic children without family history

Age (years)	IgE (U/ml)
0	7.2±2.23
1	9.1±1.96
2	11.1±1.72
3	13.0±1.50
4	15.0±1.34
5	16.9±1.24
6	18.8±1.22
7	20.8±1.30
8	22.7±1.44
9	24.7±1.64
10	26.6±1.88
11	28.6±2.14
12	30.5±2.42

IgE and air pollution

Table 5 shows the effect of air pollution on the IgE values of a non-allergic childhood population. The area was divided into three parts, depending on the level of sedimentary material. The IgE mean increased with the concentration of air pollution. The results of the statistical study were significant for a confidence level of 95%.

The samples were then divided into four groups: children with and without FHA in a polluted and non-polluted area. The presence of sedimentary material above 300 mg/m²/day was considered a polluted area.

Table 6 shows that the mean IgE value increased from the lowest value (non-polluted areas and children with non-allergic history) to the highest IgE value (children with FHA, living in polluted areas). Regarding IgE values in

Table 4
Sex influence of IgE values

	N	IgE	Mean log.	Variance
Males	185	19.2	2.9524	1.5118
Females	178	16.8	2.8198	1.3652
ts = 1.0548 (non-significant)				

Table 5
Influence of air pollution on IgE values

Group	N	IgE	Mean log.	Variance
Grade 0	167	15.49	2.7402	1.5476
Grade 1	34	18.36	2.9103	1.0056
Grade 2	162	20.78	3.0340	1.3927

Grade 0: < 300 mg/m²/day; Grade 1: 300–600 mg/m²/day; Grade 2: > 600 mg/m²/day.

Table 6
Influence of air pollution on IgE values

	Non-polluted area		Polluted area		
Without FHA	12.70	2.5418	16.49	2.8028	ts = 1.775 ($P < 0.05$)
		1.4170		1.2220	
		121		123	
With FHA	26.10	3.2621	28.98	3.3669	ts = 0.466 (NS)
		1.5459		1.3087	
		46		73	
	ts = 3.450		ts = 3.403		
	($P < 0.0005$)		($P < 0.0005$)		

The distribution of the data described above is as follows: IgE; Mean log.; Variance; No. cases.

polluted and non-polluted areas, the influence of FHA was evident, since the random probability was very low (*P* < 0.0005). On the other hand, the effect of air pollution was preferentially seen in children without FHA. In this group, the IgE mean value increased significantly in polluted living areas (*P* < 0.05). However, although the IgE mean value in children with FHA was higher in polluted than in non-polluted areas, the difference was not large enough to be considered significant. Data suggest that pollution also affected the IgE values, but the variance of the data and the small number of samples prevented any statistical treatment.

Finally, Table 7 shows that the differences in the IgE mean values found in a non-allergic population of children with FHA can not be caused by age variation in any of the studied groups.

DISCUSSION

The literature describes large variations in the IgE levels among individuals, even among

those showing no allergic or extra-allergic pathology.

The IgE values found in healthy adults have a range of 13-40 U/ml, depending on the authors and independent of the method of analysis used (4, 18, 24). The same variability, although smaller, was also observed in a childhood population. There is an increase in the total serum IgE values from birth until the age of 12-14; at this age the IgE values are similar to adult values (5, 17, 18).

We have studied the total serum IgE activity in a non-allergic childhood population, selected by means of a questionnaire; although skin tests would have been a more suitable method of selection, they were not used in asymptomatic children for ethical reasons. We found that the IgE values increased with age, in non-allergic children up to the age of 12, and the variation percentage of IgE by age was 81.8 %.

Considering the influence of FHA, the IgE mean values were significantly higher in children with FHA (27.82 U/ml) than in children without (14.49 U/ml). The same findings were also reported by Sears et al. (19) and Bonini et al. (3), thus supporting the theory of genetic influence on the control of the IgE synthesis. Sears et al. (19) also found that subjects with FHA in the immediate family had higher IgE values than subjects with FHA in the more distant family. However, we found no significant difference between the two groups.

When non-allergic children and children without FHA were tested, the variation in IgE values explained by age increased to 94.5 %. This confirms the hypothesis that IgE bio-

Table 7

Average age and number of cases in relation to atopic history and living area

	Polluted area		Non-polluted area	
	Age	N	Age	N
Without				
FHA	4.85	123	4.77	120
With FHA	5.65	73	4.14	47

synthesis is genetically controlled. That subjects with FHA synthesize higher amounts of IgE is probably due to hypofunction of the T-suppressor lymphocytes (10, 15). Hypofunction of the T-suppressor cells would be genetically determined through a multifactorial or polygenic inheritance, even when the exact number of loci involved is not known. On the other hand, the literature has not considered the influence of FHA on the reference values of IgE (14, 16, 17), but our data have clearly shown that FHA plays an important role and should be taken into consideration before establishing normal IgE values.

Finally, the function of air pollution on total IgE revealed higher IgE levels in children from the most polluted areas. The effect of air pollution was clearer in children without FHA: IgE increased significantly in polluted compared with non-polluted areas ($P < 0.05$). However, although the IgE value in children with FHA, was higher in polluted areas, the difference in relation to non-polluted areas was not significant. In summary, the degree of air pollution has an influence on the serum IgE values, but with far fewer effects than genetic factors, in such a way that when the latter are present, the pollution effect is unmeasurable. These data verify the conclusion reported by Bazaral et al. (1), where only 15–30% of IgE variation is caused by environmental effects, and the rest is due to genetic factors.

We found no reference in the literature to the influence of air pollution on the IgE values of a non-allergic population. So far, the studies have been carried out in asthmatic subjects showing no significant differences (23). However, many of these patients had extrinsic asthma, thus the genetic influence was sufficient to enhance the IgE values to a level at which it was impossible to observe the pollution effect. In addition, some studies have shown the relationship between the habit of smoking and high levels of IgE (6, 22). The high values in smokers were explained by three different factors: increase in the bronchial mucous membrane permeability to different allergens produced by cigarette smoke, increase in the number of respiratory infections, and finally, a decrease of the IgE

T-suppressor cell activity. Although it is not known why air pollution increases the IgE levels, similar mechanisms as shown in smokers, may offer an explanation.

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