

Total Serum IgE Levels in Normals and Patients with Chronic Non-Specific Lung Diseases

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Total serum IgE was measured, using a sensitive sandwich method, in a healthy control population, in healthy persons with a familial history of chronic non-specific lung disease and in patients with chronic non-specific lung disease (CNSLD). In the control population a median total serum IgE of 39 I.U./ml was found. Total serum IgE levels were significantly lower in women than in men. Healthy persons with a familial history of CNSLD had significantly increased total IgE levels compared with the control population. The IgE level was even higher in the group of patients with CNSLD. The presence of specific IgE antibodies and/or an early onset of the symptoms of CNSLD was accompanied by higher total serum IgE levels compared with the IgE values in the other CNSLD patients. But the total IgE levels were increased in all subgroups of CNSLD patients. A significant decrease of the IgE level with age was observed in CNSLD patients.

Key words: allergy; chronic non-specific lung disease; familial history; IgE; reference population.

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Chronic non-specific lung diseases (CNSLD) include bronchial asthma, chronic bronchitis and emphysema. The pathogenesis of these disorders is still unknown. Hereditary and exogenous factors influence both the development and the symptomatology. The IgE-mediated, type I hypersensitivity has been associated with bronchial asthma (9). Recent technical improvements in the dosage of total serum IgE have resulted in a more sensitive sandwich radioimmunoassay technique (3). We report the results of total serum IgE dosage in a normal population, in normal persons with a familial history of CNSLD and in patients with CNSLD.

SUBJECTS AND METHODS

Subjects

Control population. 225 healthy persons, 85 women and 140 men, were selected for the

normal population. The age varied from 19 to 66 years, the median age being 33 years. All persons had a negative personal history of allergy and CNSLD. None was taking medication at the time of blood sampling or had a recent infection. All persons included in the reference population also had a negative familial history of CNSLD.

Their serum was analysed with the RAST, using eight different allergens, to exclude the presence of specific IgE antibodies. None had specific IgE antibodies to the eight allergens tested.

Normal persons with a positive familial history. Sixty healthy persons, 16 women and 44 men, were selected for this group. The age distribution was comparable to the control population. All persons had a negative personal history of allergy and CNSLD and a negative RAST to the eight allergens tested. They all had a positive familial history of CNSLD. The familial history included parents, brothers or sisters, and children.

Patients with CNSLD. 270 patients with CNSLD, 115 women and 155 men, were included in the study. The age varied from 14 to 76 years, the median age being 37 years. All patients had a reversible airways obstruction (more than 15% increase of their FEV₁ after inhalation of fenoterol). No signs of infection were present at the time of investigation.

Methods

Total serum IgE dosage. Total serum IgE was measured using the sandwich method. Paper discs (diameter 5 mm, weight 2 mg) were punched out of Munktell 00H-filter paper. The discs were activated with CNBr, using the method described by Ceska & Lundkvist (3). The gammaglobulin fraction of 1 ml sheep anti-human IgE antiserum (Pharmacia, Sweden) was coupled to 1 g activated paper discs. The assay was performed by adding 50 μ l diluted serum and 100 μ l buffer (0.05 M phosphate buffer pH 7.9 containing 0.9% NaCl, 0.3% human serum albumin, 0.05% NaN₃ and 0.5% tween 20) to a polystyrene tube containing an anti-IgE paper disc. Samples were diluted 1/5 or 1/10 with buffer. All samples were determined in duplicate. The tubes were stoppered and shaken during 3 h at room temperature. The discs were then washed three times with 2.5 ml physiological saline.

100 μ l I¹²⁵ labeled anti-IgE (Pharmacia, Sweden) was subsequently added to the washed discs. The tubes were stoppered again and shaken overnight. A final washing with three times 2.5 ml physiological saline was done in the morning. The radioactivity remaining on the discs was then counted in a gamma counter.

A serum pool, calibrated against the WHO 69/204 reference standard, was used as standard. The IgE values were calculated from the standard curve using a Computer Automation-computer.

All samples were run in duplicate. The intra-assay coefficient of variation was 5%.

The inter-assay coefficient of variation was 12%.

Skin tests. Skin tests were performed with 12 different allergens (Bencard) by intracutaneous or prick testing. House dust, house dust mite, mixed danders, cat dander, dog dander, horse dander, fabrics, feathers, *Aspergillus fumigatus*, grass pollen, tree pollen and shrub pollen were used as antigen. Only clear-cut reactions were regarded as positive, i.e. weal reaction of more than 10 mm after intracutaneous testing or more than 2 mm after prick testing. A control reaction with Coca's fluid was included so that skin hyperreactivity could be excluded.

Bronchial challenge tests. Bronchial challenge tests with allergen were performed as described previously (16).

Dosage of specific IgE antibodies. Specific IgE antibodies were measured using the Radio Allergo Sorbent Technique (18). Allergens were coupled to activated paper discs using the same procedure as for the preparation of anti-IgE discs. The same allergens, used in the skin test, were coupled to the discs. The assay was performed exactly as described for the measurement of total serum IgE. The RAST was regarded as positive when the radioactivity remaining on the discs exceeded at least twice the radioactivity of discs incubated with sera of non-allergic persons. All samples were run in duplicate.

Statistics: The non-parametric Wilcoxon's signed rank test was used for statistical evaluation.

RESULTS

Total serum IgE levels in the control population

The total serum IgE levels in the control population were not normally distributed, even after logarithmic transformation. The median value was 39 I.U./ml with a spread from 0.09 to 3560 I.U./ml (Fig. 1 and Table 1). The 5th percentile value was 3

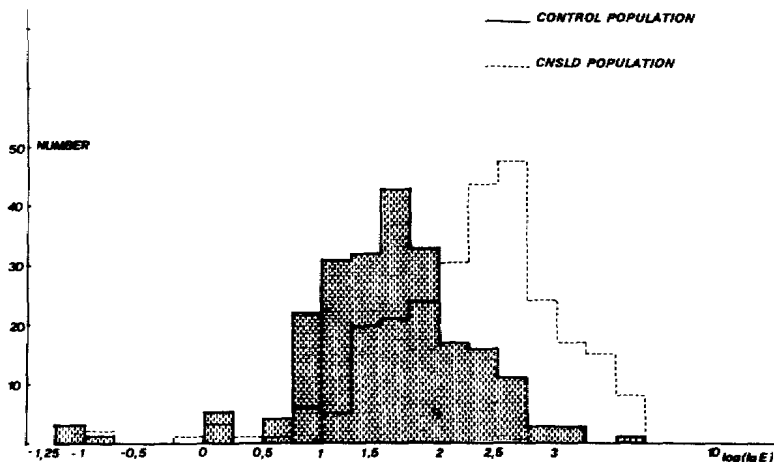


Fig. 1. Distribution of total serum IgE levels in the control population and in the group of patients with CNSLD.

Table 1

Total serum IgE levels in the different populations

	Normal population	Healthy but familial history of CNSLD	CNSLD
Number	225	60	270
Median	39 I.U./ml	65 I.U./ml	232 I.U./ml
5th percentile	3 I.U./ml	2.2 I.U./ml	9 I.U./ml
95th percentile	423 I.U./ml	570 I.U./ml	2250 I.U./ml

I.U./ml and the 95th percentile 423 I.U./ml. No significant effect of age on total serum IgE levels in normal persons could be demonstrated (Fig. 2). There was, however, a significant difference between men and women in the control population ($P < 0.02$). Normal women had a lower total serum IgE level. This difference between women and men is illustrated in Fig. 3 by showing the cumulative frequency curves in both sexes.

Total serum IgE levels in healthy persons with a familial history of CNSLD

Healthy persons with a negative personal history but a positive familial history of CNSLD had significantly increased total serum IgE levels compared with the control

population ($P < 0.05$). The median value was 65 I.U./ml with a spread from 1 to 1300 I.U./ml. (Table 1). The difference between this group and the normal population is illustrated in Fig. 4.

Total serum IgE levels in patients with CNSLD

Patients with CNSLD had a median total serum IgE value of 232 I.U./ml. This is significantly different from the normal population ($P < 0.01$) and from the group of healthy persons with a familial history of CNSLD ($P < 0.01$).

Values were spread between 0.1 and 4000 I.U./ml, the 5th percentile being situated at 9 I.U./ml and the 95th at 2250 I.U./ml. The IgE values were not distributed normally

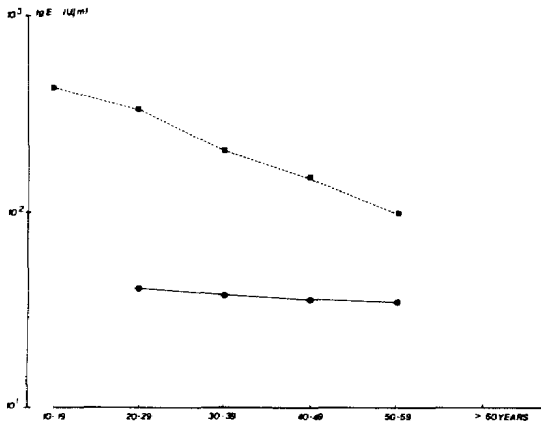


Fig. 2. Influence of age on total serum IgE levels (median values) in the control population (●) and in the group of patients with CNSLD (■).

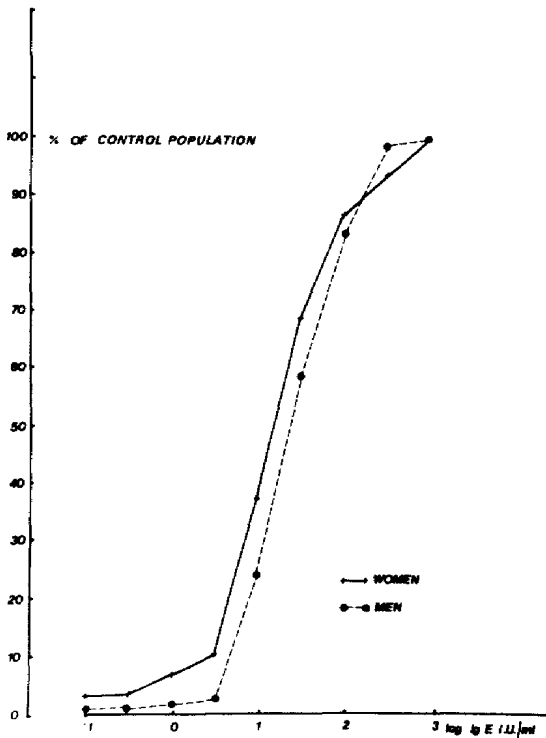


Fig. 3. Cumulative frequency of total serum IgE levels in normal men and women.

even after logarithmic transformation (Fig. 1). The presence of specific IgE antibodies, demonstrated by skin tests, bronchial challenge tests or RAST, was accompanied by a significantly increased total serum IgE level (Table 2) compared

with the patients with CNSLD without specific IgE antibodies. Both groups had, however, an increased total serum IgE level compared with the normal population. When the whole group of patients with CNSLD was divided according to the age at

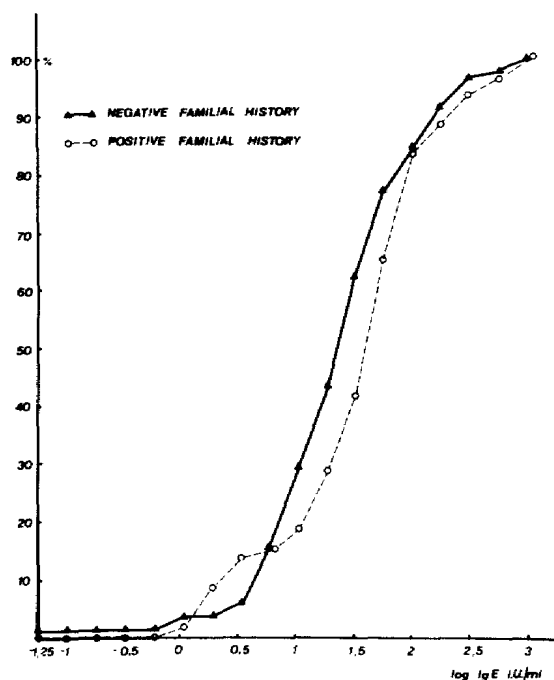


Fig. 4. Cumulative frequency of total serum IgE levels in the control population and the group of healthy persons with a positive familial history of CNSLD.

Table 2

Total serum IgE levels in patients with CNSLD

	Total group	Skin test		RAST		Bronchial challenge	
		Positive	Negative	Positive	Negative	Positive	Negative
Number	270	138	68	109	115	58	32
Median (I.U./ml)	232	333	71	467	78	410	190
5th percentile (I.U./ml)	91	27	1	29	3	49	27
95th percentile (I.U./ml)	2250	2270	2000	3250	690	2270	579
Comparison with control population	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$

Table 3.

Total serum IgE levels in patients with CNSLD dependent of the age at which the symptoms appeared

	Under 15 years	15-29 years	Above 30 years
Number	90	82	96
Median (I.U./ml)	445	200	119
5th percentile (I.U./ml)	10	23	1
95th percentile (I.U./ml)	3250	2000	1100

which the first symptoms of airways obstruction appeared (Table 3) then total serum IgE levels decreased progressively with the age of onset of the symptoms.

There was no significant difference in total serum IgE between women and men with CNSLD. Total serum IgE decreased significantly with age in the patients with CNSLD (Fig. 2) but, compared with the normal population, was high even at advanced age. The total serum IgE level was significantly higher in the second and third decade compared with the fourth, fifth and sixth decade ($P < 0.01$).

DISCUSSION

Until now, most studies on total serum IgE levels in patients with CNSLD have been done using either the radioimmunosorbent technique or the radioactive radial immunodiffusion. Both methods have such a low limit of detection that they are too high for measuring all serum IgE values. This has resulted in an overestimation of the normal serum IgE level in most studies. Only the double antibody method and the direct sandwich method are reliable for the lowest serum IgE values (11, 7). Gleich et al. (6) using the double antibody method, found a median serum IgE value of 80 ng/ml in their normal population. Since 1 I.U. equals 2.4 ng (1), their median value is situated at 33 I.U./ml. Nye et al. (14) used the same technique in their study of a normal population but for unexplained reasons they excluded the five highest values found from their calculation. Johansson (10) using the direct sandwich method, found a geometric mean serum IgE value of 13.8 I.U./ml in a group of 250 normal persons. Our control population had a median total serum IgE value of 39 I.U./ml with a large spread of the results and a distribution which significantly deviated from the normal distribution, even after logarithmic transformation.

We found a significant difference in total serum IgE levels between men and women.

Women had lower IgE levels. This difference in IgE level between both sexes has been described recently (5). Sex differences have also been observed for serum IgM, IgG and IgD (12) where women have higher values than men.

Patients with chronic non-specific lung diseases, including bronchial asthma, chronic bronchitis and emphysema, had an increased total serum IgE level even in the absence of specific allergy. The presence of specific allergy was accompanied by a still higher total IgE. These results agree with the earlier findings of Debelic et al. (4) and Reerink-Brongers et al. (7) who used a less sensitive technique. Our findings suggest that CNSLD and an increased total serum IgE level are linked together. The fact that normal persons with a positive familial history of CNSLD had also an increased total serum IgE is further evidence for this hypothesis. Both CNSLD and total serum IgE levels are under genetic control (15, 2, 13). Our results thus suggest a closely linked or common genetic control for CNSLD and the total serum IgE level. Other factors, both endogenous and exogenous may then control the production of specific IgE antibodies.

The total serum IgE in the normal population did not change significantly with age. Patients with CNSLD, however, showed a decreasing total serum IgE level with age. This may be due to a decrease in the frequency of specific IgE antibodies with age (8).

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