

From the Department of Allergology, Sahlgren's Hospital, University of Göteborg, and the Blood Center, University of Uppsala, Sweden.

IMMUNOGLOBULIN E IN BRONCHIAL ASTHMA

By

B. ELGEFORS, A. JULIN & S. G. O. JOHANSSON

The introduction of the radioimmunosorbent technique (RIST) (18) for quantitation of IgE gave the clinician another tool in the diagnosis of asthma. Preliminary studies indicated that high IgE values occurred in a large proportion of patients with extrinsic asthma (7). Later reports (4, 17) did not give such conclusive results.

As the selection of patients is of great importance in analysis of asthma, as well as for other diseases, we thought it would be interesting to analyze IgE in a randomly selected, well-defined population of patients (from our outpatient clinic) with intrinsic or extrinsic asthma. These patients were also studied during hyposensitization. In a previous paper we reported the serum levels of IgG, IgA and IgM in patients drawn from the same population (3).

PATIENTS

For a detailed analysis of the study population of 223 patients, selected at random, the reader is referred to the report of Julin (9). The purpose of that study was an analysis of asthma from the points of view of allergology, sociology, psychology and psychiatry. The patients were drawn at random from a population of 1,200 cases of bronchial asthma, who during 1968 were treated as outpatients at the Department of Allergology, Sahlgren's Hospital, Göteborg. All these patients had controls, matched with respect to age and sex using data from the population register in Göteborg.

The classification of the patients was the same as previously described (3). Of patients with intrinsic asthma, only those 58 earlier presented (3) were analyzed. As most of the patients with extrinsic asthma were treated by hyposensitization,

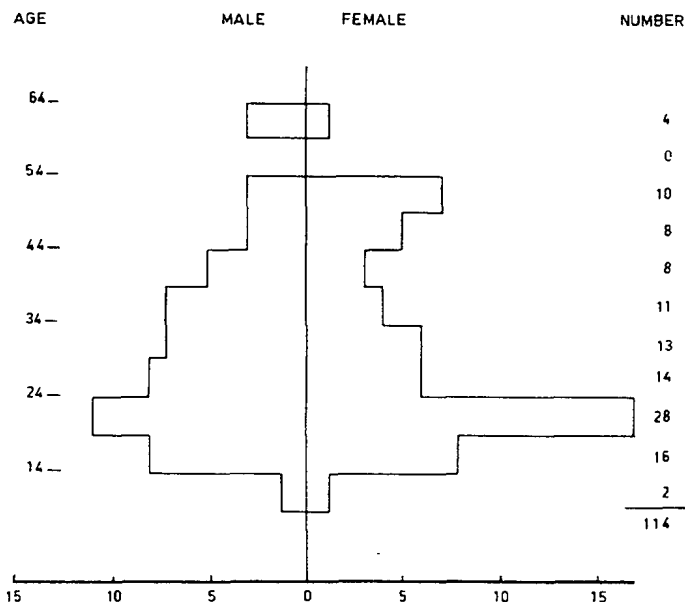


Fig. 1.

Age- and sex-distribution of 114 patients with extrinsic asthma.

another 30 non-hyposensitized patients were added from the year 1970–1971 in order to analyze the influence of this treatment. These patients were analyzed at their first visit to the clinic, but had no matched controls and were not studied in respect of other diseases. Using the Kolmogorov-Smirnov and median split tests (14), no significant differences were observed between the initial group and the added patients when IgE and age were used as variables. It was then thought to be fair to bring these two groups together in the analyses which followed. The total group of patients with extrinsic asthma and IgE determinations thus comprised 114 patients, with sex- and age-distribution as in Fig. 1. Mean age was 31.4 years and median age 27.8 years. Fifty-one per cent were female.

A heredity of asthma was considered to be present when at least one of parents, brothers, sisters or children had asthma. This was observed in 55 cases. Eosinophilia, with more than 400 cells/mm³ according to Rud (12) or more than 5 per cent in differential counts, was present in 44 cases. The number of patients with an allergy to dust was 63, mold 21, animal danders 54, and pollen 54.

Fifty-seven patients were allergic to two or more categories of allergens. Ninety-four had an atopic disease in addition to asthma. Among 84 patients, a history of allergic disease (other than asthma) was found with the following frequencies: pollenosis in 41 per cent (controls 6.8 per cent); allergic rhinitis of other origin than pollen in 42 per cent (3.4 per cent); Quincke oedema in 10 per cent (1.1 per cent); and other allergic skin diseases in 61 per cent (22 per cent). The patients were analyzed in their habitual state with moderate bronchial obstruction. Spirometry recorded with a Vitalograph® gave a forced expiratory volume in one second (FEV₁) of 2.99 liters (controls 3.48), or expressed per cent of predicted values, 78 per cent (92 per cent). Blood samples were drawn without reference to seasons or seriousness of disease.

METHOD

Serum IgE was determined with RIST (8) at the Blood Center, University of Uppsala. All samples had been frozen and were thawed before analysis. As a

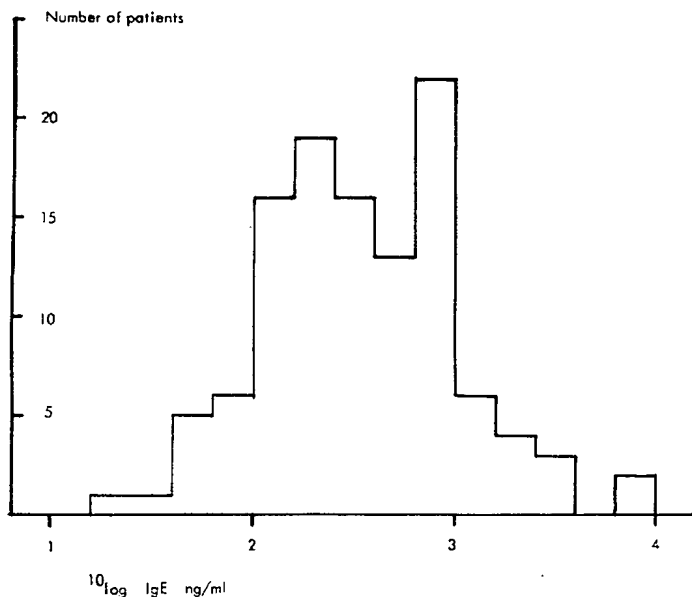


Fig. 2.

The logarithmic distribution of the IgE values for 114 patients with extrinsic asthma.

normal value for IgE, an upper quantile of 700 nanogram/ml was used, and this was somewhat lower than two standard deviations above the mean value (813 ng/ml) for the control subjects.

Statistics

The IgE values did not fit the normal distribution, and accordingly non-parametric tests were used: a modified Wilcoxon test and Chi-square analysis. For characterization of the different subgroups, the median was used and as a measure of deviation, the extreme values and the percentage above 700 ng/ml. The 0.05 level of significance was used. As some of the patients were without matched controls, and some of the controls had very high IgE levels, the control subjects were analyzed as a group and not as individuals in comparison with the matched pairs.

RESULTS

The 114 patients with extrinsic asthma had a median IgE of 337 ng/ml, and a range of 24-8838 ng/ml. The corresponding values for the group with intrinsic asthma was 168 (30-3550) ng/ml, and for the controls 173 (41-1900) ng/ml. Fig. 2 shows the distribution of the IgE values, and Table 1 the means, standard deviations and quantiles. Of the 114 patients with extrinsic asthma, 30 per cent had values exceeding 700 ng/ml, which significantly differed from both the intrinsic group with 7 per cent, and the control group with 5 per cent (Chi square 9.8 and 19.0).

The four patients with intrinsic asthma and high IgE levels were reexamined and retested, but no exogenous factors were detected.

TABLE 1

Analysis of IgE Values for 172 Patients with Bronchial Asthma and 99 Controls.

Diagnosis	Number	Frequency exceeding 700 ng/ml	Median ng/ml	Mean ng/ml	SD ng/ml	Range ng/ml
Extrinsic asthma	114	34 (30%)	337	692	1160	24-8838
Intrinsic asthma	58	4 (7%)	168	280	487	30-3550
Control subjects	99	5 (5%)	173	265	274	41-1900

TABLE 2
Analysis of Factors Possibly Influencing IgE Levels.

Patients with:	Number of patients	Median IgE ng/ml	Per cent exceeding 700 ng/ml
Heredity of asthma	55	375	31
Eosinophilia	44	476	39
Dust allergy	63	404	30
Mold allergy	21	375	48
Animal allergy	54	355	22
Pollen allergy	54	430	33
Total	114	337	30

In Table 2, some factors which might be of importance for the IgE levels are analyzed. High eosinophil leukocyte counts and allergy towards molds correlated best with high IgE levels. Only for mold allergy was this increase significant. One allergic disease in addition to asthma hardly influenced the IgE median, but the concomitant existence of allergic rhinitis and eczema raised the median IgE from 239 to 590 ng/ml, and the percentage above 700 ng/ml from 20 to 38 per cent.

Sensitivity to two or more categories of allergens, and the presence of allergic skin disease as well as a heredity of asthma increased the median IgE to 474 ng/ml; and eight of the 26 patients with these factors present had levels above 700 ng/ml (Fig. 3). In Table 3, the effect of hyposensitization is analyzed. Patients had, during their first year's hyposensitization, an increase of IgE which was not significant when compared to longer treated or untreated patients.

The effect of age on IgE was not discernible, and a moderate IgE depression at about 45 years was not significant. Neither could any differences due to sex be established.

DISCUSSION

The unique range of the IgE values has been an obstacle in the analysis and comparison of different investigations. High IgE

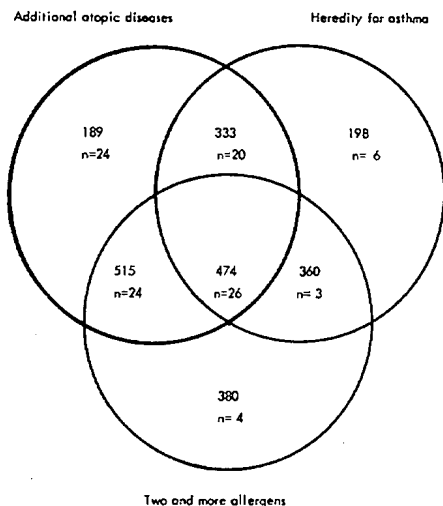


Fig. 3.

Median IgE in $\mu\text{g/ml}$ and number of patients distributed according to presence of atopic diseases except asthma, heredity for asthma, and multiple allergens.

values are included in the normal values since it is impossible to find reasons to exclude apparently healthy persons from normal materials. Table 4 shows the correlation between the discriminatory IgE values used by different authors and the frequency of pathological findings. Our figure of 30 per cent

TABLE 3
Analysis of the Effect of Hyposensitization on IgE Levels.

Hyposensitization	Number of patients	Frequency exceeding IgE 700 ng/ml	Median IgE ng/ml
Not performed	44	25%	248
0-1 years	21	43%	585
1-3 years	26	27%	359
Completed	23	30%	315

TABLE 4

Summary of Results from the Literature on IgE in Extrinsic Asthma.

Author	Year	Number of patients tested	Upper normal level of IgE ng/ml	Per cent above the normal level
Johansson	1967	16	700	63
Heiner & Rose	1970	19	800	68
Gleich et al.	1971	133	1000	35
		"	800	48
Henderson et al.	1971	30	540	76
Virchow et al.	1972	41	250	71
Dahlström et al.	1973	29	300	59
Elgefors et al.	1974	114	700	30

with pathological values in extrinsic asthma is the lowest recorded; but setting the discriminatory level below 700 ng/ml would be incorrect since this level is already lower than the two standard deviations above the mean customarily used. The investigation of Gleich et al. (4) was based on 133 patients and agrees most closely with ours.

Berg & Johansson (1) found IgE increased as hyposensitization started, and then later decreased. Gleich et al. did not find any difference between untreated and treated (hyposensitized) patients, and our differences were not significant either although IgE seemed to increase during the first year of hyposensitization. From the theory of blocking antibodies already put forward by Sherman in 1957 (13), and from animal experiments, where a consumption of reagins has also been suggested (15), a decrease might have been expected after hyposensitization. However, our study was not designed for this kind of analysis, since the individual patient was not analyzed during the course of his disease.

Mold and animal danders were allergens connected with high IgE levels in the study of Virchow et al. (16). In our study, mold allergy was also connected with high IgE. Most patients with mold allergy had other proven allergies too. The conclusions are therefore obscure, since it has been shown that

the total level of serum IgE is more dependent on the number of allergens than their categories (6, 17). Our analysis comprised only different types of allergens, and the influence of different subgroups within the pollen group was not analyzed. For such an analysis the specific reagins must be analyzed (17).

IgE level was not found to be affected by age or sex differences in this study, but patients under 9 or above 64 years of age were not studied. As was pointed out earlier, the diagnosis of intrinsic asthma is made by exclusion. Only 7 per cent of these patients have high IgE values—the same figure as in Dahlström et al. (2)—which might indicate that intrinsic asthma has a different pathogenic mechanism, and is not caused by hidden and as yet undetected allergens. It seems that the use of RIST to discriminate between extrinsic and intrinsic asthma is restricted for various reasons: e.g. the majority of patients with extrinsic asthma had low IgE levels; some of the controls had extremely high values without any signs of disease; and parasite infestation (1, 10) and other diseases (5) might influence the levels. Nevertheless, if high levels are found in a patient a further search for allergens may be rewarding. In order to optimize the information from IgE quantitation, it is necessary to define the activity of asthma, other atopic diseases, type of allergy, treatment with hyposensitization, and heredity. The clinical examination of an allergic patient has long been based on history, skin tests and provocations, and quantitation of IgE is complementary to these diagnostic foundations.

SUMMARY

Quantitative IgE determinations were performed on a randomly selected population of bronchial asthma patients from an out-patient clinic, and on matched controls. Thirty per cent of 114 patients with extrinsic asthma had levels above 700 ng/ml, while the frequency for patients with intrinsic asthma was 7 per cent, and for controls 5 per cent.

High eosinophil leukocyte counts, allergy towards mold, co-existing allergic rhinitis and eczema all correlated with high IgE levels. There was no conclusive evidence that hyposensitization has an effect on IgE levels. IgE quantitation may in some cases support the diagnosis of allergy, and form a basis for further investigations.

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Author's address:

*B. Elgefors,
Östra Sjukhuset,
S 416 85 Göteborg,
Sweden.*

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