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NEW IMMUNOGLOBULIN CLASS (IgND)
IN ASTHMA

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Summary Significantly raised serum levels of a new class of immunoglobulins, provisionally called IgND, were found in 63% of patients with allergic asthma compared to 5% of patients with non-allergic asthma. Mean concentration of IgND was 6 times higher in the group with allergic asthma than in the group with non-allergic asthma. These findings are of particular interest since IgND has many characteristics in common with reagins. No differences were found between allergic and non-allergic patients with respect to the concentration of the immunoglobulins A, D, G, or M in the serum.

Introduction

RECENTLY studies of an atypical myeloma protein (Johansson and Bennich 1967a) and its normal counterpart (Johansson, Bennich, and Wide 1968) were reported. It was shown that the immunoglobulin did not belong to any of the classes IgA, IgD, IgG, or IgM. This new class of human immunoglobulins was provisionally called IgND. The immunological (Johansson and Bennich 1967a, Johansson, Bennich, and Wide 1968, Johansson and Bennich 1967b) and physico-chemical (Johansson and Bennich 1967a, Bennich and Johansson 1967) properties of IgND are very similar to those of reagins (Stanworth 1963), and raised levels of IgND were found in sera from patients with asthmatic bronchitis and hay-fever (Johansson and Bennich 1967b) compared to levels in healthy individuals (Johansson, Bennich, and Wide 1968). It was shown that isolated myeloma-IgND could specifically inhibit the Prausnitz-Küstner reaction (Stanworth, Humphrey, Bennich, and Johansson 1967).

Preliminary comparative studies (Johansson, Bennich, Ishizaka, and Ishizaka 1967) indicate that there is an

antigenic relationship between IgND and the reaginic antibodies to ragweed allergen E, γ E-globulins, extensively studied by Ishizaka et al. (1966)

The present study deals with the IgND distribution in sera from an unselected sample of asthmatic bronchitics in relation to the clinical diagnosis.

Material and Methods

From the department of lung diseases, Hospital of Eskilstuna, Eskilstuna, Sweden, serum samples from 38 cases were kindly provided by Dr. I. Sjögren. According to the clinical diagnosis, based upon skin and provocation tests as well as on the history and physical examination, the samples were classified as follows:

A, "Allergic type" (skin and provocation tests positive).—This group consisted of 16 patients (6 male and 10 female); mean age 35 years, median age 34 years, age range 12–72 years.

B, "Non-allergic type" (no allergy demonstrated: i.e., skin and provocation tests negative).—Sera from 22 patients (7 male and 15 female); mean age 52 years, median age 55 years, age range 8–71 years.

The allergy tests were performed with 15 commercial allergens (Vitrum AB, Stockholm) including 4 pollen mixtures and 9 animal dandruffs, mould, and dust. 5 patients (2 group A and 3 group B) received corticosteroids in small or moderate doses. 6 patients (5 group A and 1 group B) had been treated with a single short-time hyposensitisation six months to eighteen years before the sample was drawn. One patient received γ -globulin injections; his IgG value is not included in the calculations.

Samples were collected by venepuncture and the sera were stored at -20°C until analysed. All sera were tested by immunoelectrophoresis with a polyvalent immunoglobulin antiserum for qualitative analysis, and by single radial diffusion in gel for the quantitative determination of the immunoglobulins A, D, G, and M (Johansson, Högman, and Killander 1967). IgND was determined by an inhibition technique, the radio-immunosorbent assay (R.I.S.A.) (Johansson, Bennich, and Wide 1968).

Statistical analyses were done using Student's *t* test on the numerical values. The immunoglobulin levels did not distribute in a gaussian manner. In order to normalise the distribution the values were also transformed logarithmically to base 10 before statistical analysis. Since this gave the same results as analysing non-transformed values, only those are given here.

Results

The concentrations of the immunoglobulins A, D, G, and M are given in table 1. There is no significant difference between the mean values in group A and B for any of these immunoglobulins, but the whole asthma group has a significantly ($P < 0.001$) lower IgD mean level than the normal group.

As can be seen from the accompanying figure there seems to be two categories of samples in respect to the

TABLE I—SERUM LEVELS OF THE IMMUNOGLOBULINS A, D, G, AND M IN: A, ALLERGIC ASTHMA; AND, B, NON-ALLERGIC ASTHMA (CONCENTRATION IN mg. per 100 ml.; RANGE IN PARENTHESES)

Group	IgA		IgD		IgG		IgM	
	Mean	s.d.	Mean	s.d.	Mean	s.d.	Mean	s.d.
Asthma, total ..	144 (65.0-272)	59.1	4.3 (<1-12.4)	4.3	1068 (325-1965)	350	77.2 (19.5-235)	39.9
A, Allergic ..	140 (54.5-272)	63.9	4.5 (<1-15.2)	4.6	1113 (325-1795)	382	74.4 (21.0-235)	51.2
B, Non-allergic ..	146 (65.0-257)	56.4	4.1 (<1-19.4)	4.1	1086 (777-1965)	250	79.2 (19.5-140)	30.5
Normal *	158 (50.8-379)	60.5	11.7 (<1-55.7)	10.4	1323 (756-2210)	279	88.4 (20.6-279)	43.4

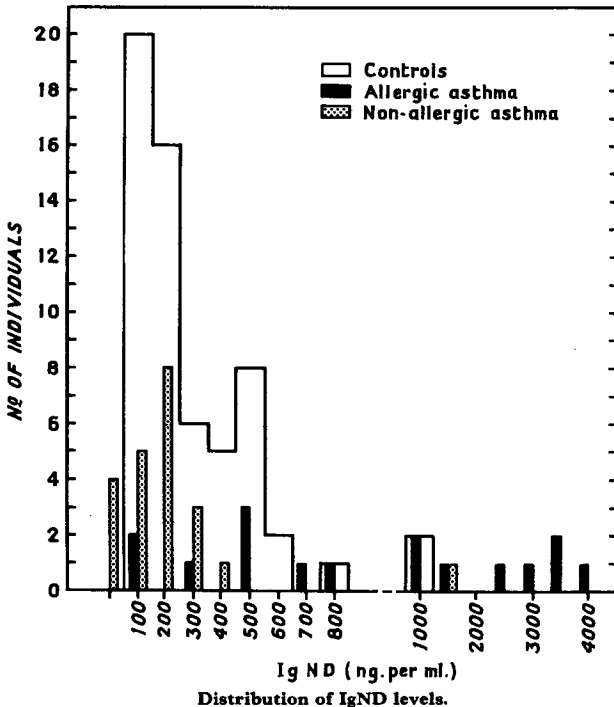
* Analyses on sera from 89 individuals, 20-70 years of age and with an even sex and age distribution, chosen to represent a Swedish normal population. (From Johansson, Högman, and Killander 1967.)

TABLE II—SERUM LEVELS OF IgND IN: A, ALLERGIC ASTHMA; AND B, NON-ALLERGIC ASTHMA. (CONCENTRATION IN ng. per ml.; RANGE IN PARENTHESES)

No.	Mean	s.d.	< 700 ng. per ml.	> 700 ng. per ml.
Asthma, total (38) ..	828 (49-4033)	1146	27 (71%)	11 (29%)
A, Allergic (16) ..	1589 (122-4033)	1433	6 (37%)	10 (63%)
B, Non-allergic (22)	275 (49-1510)	293	21 (95%)	1 (5%)
Normal * (61) ..	330 (105-1394)	236	58 (95%)	3 (5%)

* Sera from healthy blood-donors. (From Johansson, Bennich, and Wide 1968.)

distribution of IgND levels; 700 ng. per ml. was selected as the arbitrary limit. The frequency of samples belonging to groups A and B in respect to this limit is given in table II. 10 out of 16 (63%) samples in group A were found above 700 ng. per ml. compared to 1 out of 22 (5%) in group B. The IgND concentrations in the two groups, compared to normal, are given in table II. The difference in the mean IgND level between group A and



B is statistically significant, $P < 0.001$. There were no significant differences in IgND levels between the steroid and hyposensitisation treated patients and those not so treated. No age difference for IgND was observed.

Discussion

It is rather uncommon for a certain type of antibodies to be restricted to only one class of immunoglobulins. The reagins, however, have some characteristic functions and physico-chemical properties which have given rise to the suggestion that they might belong to a special immunoglobulin class (Stanworth 1963). There have been great difficulties in isolating and characterising this proposed immunoglobulin, and so far the work of Ishizaka et al. (1966) on reagins to ragweed allergen E has been the most successful.

The finding of a new class of human immunoglobulins, IgND, which has many characteristics in common with reagins justifies the study of immunoglobulin levels in sera from allergic and non-allergic patients. Much-raised levels of IgND were found in sera from patients with allergic asthma, the mean level in patients with proven allergy being 6 times that of the control group. As many as 10 out of 16 (63%) of the patients with allergic asthma had raised IgND concentrations, compared to 1 out of 22 (5%) of those with non-allergic asthma. This single case with a raised IgND concentration classified as non-allergic asthma may well be an allergic case which is wrongly diagnosed owing to the limited number (15) of allergens used for the tests. No differences were found between allergic and non-allergic patients in serum levels of the immunoglobulins A, D, G, or M. The report by Kohler and Farr (1967) of high IgD levels in sera from allergic patients could not be verified. The mean IgD level was lower in the two groups of asthmatics together (4.3 mg. per 100 ml.) than in normals (11.7 mg. per 100 ml.). This might be due partly to a higher frequency (16/25; 64%) of women above 50 years of age than in the normals (19/47; 40%). It has been shown that in healthy women the IgD level is significantly lower after the fertile age than in the fertile age (Johansson, Högman, and Killander 1967).

Most of the patients studied were tested before hyposensitisation. In a few cases a single course of hyposensitisation had been given six months to several years before the sample was taken. Preliminary studies show that the IgND concentration in a single patient sometimes, but not always, rises during such therapy (Johansson and Bennich 1967c). Even higher IgND levels might therefore be found in treated patients. The influence of steroids on the IgND serum level is not known. As

Wollheim (1967) showed, the levels of the immunoglobulins A, G, and M may vary quite differently during such therapy.

Reagin titres have been reported to be higher during a period with symptoms than during a symptom-free period (Levy 1967). In the present study the day of taking the sample has not been evaluated in relation to the patient's symptoms.

There is a tendency to lower age in the group with allergic asthma, who had a mean age of 35 years, compared to 52 for the control group. However, there is great overlap, the age range for allergic patients being 12-72 years compared to 8-71 years for the non-allergic patients.

Raised levels of IgND have been found not only in cases of asthma and hay-fever, but also in cases of Wiskott-Aldrich syndrome (Berglund, Finnström, Johansson, and Möller 1967), and atopic eczema (Johansson and Bennich 1967c).

So far as the immunoglobulins A, D, G, and M are concerned, it is unusual that an increase in the formation of a specific antibody is reflected in a significant elevation of the immunoglobulin level due to this specific antibody. This may be more prone to happen with IgND, whose normal level is only about 1/40,000 of that of IgG and 1/5000 of that of IgA. Further studies may elucidate whether the elevated levels of IgND represent an increased concentration of specific reaginic antibodies or are due to formation of non-specific IgND protein.

I wish to thank Dr. I. Sjögren for kindly supplying the samples. This work was supported by grants from the Swedish Medical Research Council (no. B 68-16X-105-04) and from the Faculty of Medicine, University of Uppsala.

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