

Immunoglobulin E in Immunologic Deficiency Diseases. I. RELATION OF IGE AND IGA TO RESPIRATORY TRACT DISEASE IN ISOLATED IGE DEFICIENCY, IGA DEFICIENCY, AND ATAXIA TELANGIECTASIA

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Research Article

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80% (35 of 44) of patients with ataxia telangiectasia (AT) were IgE deficient, 66% were IgA deficient, and 57% had combined IgE and IgA deficiencies. Although 45% of the patients with AT had respiratory tract disease, there was no correlation found between IgE deficiency or combined IgE and IgA deficiency and respiratory tract disease in these patients.

11 of 25 individuals with isolated IgA deficiency were also IgE deficient. All 11 patients with both IgA and IgE deficiency were uniformly asymptomatic. However, there was an extremely high incidence (71%) of respiratory tract disease in IgA-deficient individuals who were not IgE deficient. These data fail to support the concept of a protective role for IgE in respiratory tract immunity. The possible role of IgE in the pathogenesis of respiratory tract disease in [...]

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Immunoglobulin E in Immunologic Deficiency Diseases

I. RELATION OF IgE AND IgA TO RESPIRATORY TRACT DISEASE IN ISOLATED IgE DEFICIENCY, IgA DEFICIENCY, AND ATAXIA TELANGIECTASIA

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ABSTRACT Serum immunoglobulin E concentration was studied in normal children and adults, in 25 patients with isolated IgA deficiency, and in 44 patients with ataxia telangiectasia using a double antibody radioimmunoassay. The geometric mean IgE level of the normal adult population studied was 105 ng/ml, with a broad 95% interval (5–2045 ng/ml). Individuals with concentrations less than 15 ng/ml were considered to be IgE deficient. IgE deficiency, defined in this way, was observed in 7 of 73 normal adults and was not found to be associated with respiratory tract disease.

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11 of 25 individuals with isolated IgA deficiency were also IgE deficient. All 11 patients with both IgA and IgE deficiency were uniformly asymptomatic. However, there was an extremely high incidence (71%) of respiratory tract disease in IgA-deficient individuals who were not IgE deficient. These data fail to support the concept of a protective role for IgE in respiratory tract immunity. The possible role of IgE in the pathogenesis of respiratory tract disease in IgA-deficient patients is discussed.

INTRODUCTION

The role of immunoglobulin E (IgE) in the mediation of immediate hypersensitivity reactions in man and its

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association with asthma and other atopic diseases has been well established (1–3). The function of IgE in infectious disease processes is, however, less clear. Chronic sinopulmonary disease has been noted in a patient with isolated IgE deficiency (4) and in a patient with combined IgA and IgE deficiency (5). In addition, there is an apparent association of respiratory tract disease with combined IgA and IgE deficiency in patients with ataxia telangiectasia (6, 7). These findings have led to the suggestion that IgE itself or in combination with IgA plays an important role in the protection of respiratory tract mucosa against infection (5, 6). However, this postulate has recently been called into question by the observation of a healthy IgE-deficient individual (8) as well as the absence of IgE deficiency in IgA-deficient patients with significant respiratory tract disease (9).

The purpose of this study was to determine the serum IgE concentrations of normal children and adults, of individuals with isolated IgA deficiency, and patients with ataxia telangiectasia. Our data fail to support the concept of a protective role for IgE in the respiratory tract. On the contrary, the data suggest that the presence of IgE in individuals with isolated IgA deficiency may be associated with a high incidence of respiratory tract disease.

METHODS

Sera. 73 sera were obtained from normal adult blood donors at the National Institutes of Health Blood Bank and from laboratory personnel (age range 21–60 yr). No attempt was made to exclude individuals with a history of allergy. Sera of 71 normal nonallergic infants and children, ranging in age from birth to 15 yr, were obtained from children studied at the National Institutes of Health or provided by Doctors H. Lischner, L. Robinson, and A. B. Minnefor. Sera from 44 patients with ataxia telangiectasia

TABLE I
Serum IgE Concentration (nanograms/milliliter) in Normal and Immune Deficient Individuals

| | Number | Mean | 95% interval | P* | % <15 |
|---|--------|------|--------------|--------|----------|
| Normal adults | 73 | 105 | 5-2045 | — | 10 |
| Isolated IgE deficiency | 7 | 8 | 5-14 | — | 100 |
| Isolated IgA deficiency | 25 | 35 | 1-1396 | <0.02 | 44 (28)† |
| Ataxia telangiectasia (total) | 44 | 12 | 1-122 | <0.001 | 80 |
| Ataxia telangiectasia with IgA present | 15 | 19§ | 2-174 | <0.001 | 66 |
| Ataxia telangiectasia with IgA deficiency | 29 | 10§ | 1-93 | <0.001 | 86 |

* Geometric means of patient groups are compared with that of the normal adult population using Student's *t* test.

† The value in parenthesis is the percentage of IgE deficiency among 18 independently ascertained IgA deficient individuals.

§ The difference between these mean values is not significant, $P > 0.05$.

(AT),¹ 25 patients with isolated IgA deficiency, and 3 patients with known isolated IgE deficiency were obtained from Doctors A. J. Ammann, H. N. Claman, M. D. Cooper, P. Fireman, D. Frommel, R. A. Good, A. Lawton, D. A. Levy, H. A. Lischner, and M. L. Schulkind, as well as from our own patient population. All sera were stored frozen at -20°C before study. Information concerning exact diagnosis, clinical picture, quantitative serum immunoglobulin, and delayed hypersensitivity studies was also collected and tabulated for each patient.

Quantitation of serum immunoglobulins with the exception of IgE. The concentrations of immunoglobulins G, A, M, and D were determined by single radial diffusion in agar (10, 11).

Purified IgE myeloma proteins. A purified preparation of the IgE myeloma protein from patient N.D., was kindly provided by Doctors S. G. O. Johansson and H. Bennich. Purified IgE myeloma protein from patient P. S., was obtained from plasma (kindly provided by Dr. O. Ross McIntyre) by elution from diethylaminoethyl-cellulose (Whatman DE-52) at 0.025 M Tris-HCl, pH 8.0, and further purified by gel filtration on Sephadex G-200 columns. Protein concentrations of these purified preparations were determined by absorbance at 280 nm. $E_{280}^{1\%} = 15$ was assumed for both the P.S. and N.D. myeloma proteins.

Antisera. Antisera to IgE (P.S.) were produced in rabbits. Copolymers containing bovine serum albumin, fetal bovine serum, IgG, IgA, IgM, P.S. light chains, and agammaglobulinemic plasma, prepared by ethyl chloroformate insolubilization (12), were used to absorb the antisera and render them specific for IgE. Specificity of the antisera was confirmed by Ouchterlony double diffusion tests.

Radioiodination of IgE (N.D.). ¹²⁵I-labeled IgE (N.D.) was prepared by the chloramine-T method (13). 2 μg of purified IgE (N.D.) was added to 500-700 μCi of ¹²⁵I in the presence of 5 μg of chloramine-T. After 30-45 sec the reaction was terminated by the addition of 62.5 μg of sodium metabisulfite, and the radioiodinated protein was separated from inorganic ¹²⁵I by gel filtration on Sephadex G-100. The IgE-¹²⁵I (N.D.) thus obtained was greater than 96% trichloroacetic acid (TCA) precipitable and had a specific activity of 50-75 $\mu\text{Ci}/\mu\text{g}$. This material was satisfactory for use in the radioimmunoassay for 3-4 wk.

¹ Abbreviation used in this paper: AT, ataxia telangiectasia.

Radioimmunoassay of serum immunoglobulin E. Serum IgE was measured by a double antibody method employing specific rabbit anti-IgE (P.S.) and ¹²⁵I-labeled IgE (N.D.) (14, 15). Standard inhibition curves were obtained by the addition of known amounts of purified unlabeled IgE (N.D.) or IgE (P.S.). A standard curve was constructed for each assay by plotting the logit of the percentage of specific counts bound vs. \log_{10} nanograms of IgE added to the reaction mixture (16). These curves were linear from 0.2 to 28 ng. IgE concentration of unknown serum samples was calculated from the coordinates of the least squares regression equation of the standard inhibition curve. The average standard deviation of duplicate determinations performed on different days was 2.6%. Specificity of the assay for IgE was checked through the study of purified IgG and IgA myeloma proteins as well as sera from patients with IgG, IgA, and IgD myeloma, Waldenström's macroglobulinemia, and sex-linked recessive agammaglobulinemia.

Statistical methods. Serum immunoglobulin concentrations are not distributed in a Gaussian manner (17, 18). The logarithm to the base 10 of the immunoglobulin concentration is, however, often normally distributed (18). For this reason the geometric mean rather than the arithmetic mean was used to estimate the median values for a given immunoglobulin in a population, and the \log_{10} of the immunoglobulin concentration was used in all statistical tests. Statistical analyses were performed by Student's *t* test, Fisher's exact test for 2×2 contingency tables, and least squares regression analysis using standard methods (19).

RESULTS

IgE concentration in normal adults and children. The range of serum IgE concentration in 73 normal adults was found to be 6-18,951 ng/ml. The \log_{10} of individual serum IgE concentrations was normally distributed with a geometric mean of 105 ng/ml, and a 95% interval extending from 5 to 2,045 ng/ml (Table I).

The range of serum IgE concentrations in 71 normal children (age range, birth-15 yr) was 7-886 ng/ml. A least squares regression of \log_{10} IgE concentrations vs. age was computed from the IgE values of 57 children ranging in age from birth to 6 yr. This equation pre-

TABLE II
Association of Serum IgE Concentration and Respiratory Tract Disease

| | Serum IgE | | P* |
|---------------------------------------|-----------|-----------|---------|
| | >15 ng/ml | <15 ng/ml | |
| A. Isolated IgE deficiency | | | |
| (a) With respiratory tract disease | 0 | 1 | |
| (b) Without respiratory tract disease | 0 | 6 | — |
| B. Isolated IgA deficiency | | | |
| (a) With respiratory tract disease | 10 | 0 | |
| (b) Without respiratory tract disease | 4 | 11 | <0.0005 |
| C. Ataxia telangiectasia | | | |
| 1. All patients | | | |
| (a) With respiratory tract disease | 3 | 17 | |
| (b) Without respiratory tract disease | 6 | 18 | >0.22 |
| 2. Patient with IgA deficiency | | | |
| (a) With respiratory tract disease | 2 | 14 | |
| (b) Without respiratory tract disease | 2 | 11 | >0.39 |

* Fisher's exact test was used to determine if the presence or absence of IgE is correlated with the presence or absence of respiratory tract disease in the above patient groups. *P* values greater than 0.05 indicate no statistically significant correlation.

dicts that the geometric mean adult IgE concentration is reached by 4.3 yr of age. Since only 2 of the 76 patients studied were under 4.3 yr of age, IgE values of the patient groups were compared with the normal adult values. The two children under 4.3 yr of age were classified as either IgE deficient or normal, using the IgE vs. age regression equation mentioned above.

The range and 95% interval of the normal adult population are extremely broad and do not permit a meaningful division of patients into IgE-deficient and non-deficient groups. Approximately 90% of the normal population was found to have IgE values greater than 15 ng/ml. Therefore, to facilitate analysis and discussion of the data, individuals with IgE values falling below the 10th percentile (less than 15 ng/ml) were considered to be IgE deficient.

Isolated IgE deficiency. Serum IgE concentrations of less than 15 ng/ml were found in 7 of 73 normal adult blood donors and laboratory personnel. The geometric mean IgE concentration of the group was 8 ng/ml. One of the seven IgE deficiency individuals had a history of chronic sinusitis (Table II, A). This individual had the highest IgE level (12 ng/ml) in the IgE-deficient group. There was no history of upper or lower respiratory tract disease, asthma, or allergy in the remaining six. Quantitative immunoglobulin determinations

failed to reveal other immunoglobulin abnormalities in these seven individuals. The healthy IgE-deficient individual previously reported (8) was found to have a serum IgE concentration of 9 ng/ml by our radioimmunoassay.

IgE concentration in patients with IgA deficiency. Serum IgE concentrations were determined in 25 patients (age range 10 months–75 yr) with previously known isolated IgA deficiency^a (Table I). The mean IgE concentration of these patients, 35 ng/ml, differed significantly from that of the normal adults ($P < 0.02$). 11 of the 25 individuals in this group were IgE deficient, while the values of the other IgA-deficient individuals extended over a broad range, the highest being 4807 ng/ml. Among the 25 patients with isolated IgA deficiency, 8 individuals belonged to the same family. Therefore, of 18 independently ascertained isolated IgA-deficient patients, 5, or approximately 28%, had an associated IgE deficiency. It would appear, therefore, that IgE deficiency occurs more frequently among IgA-deficient individuals (28%) than it does in the normal population (10%). This difference is statistically significant ($P < 0.01$, binomial distribution).

11 individuals were found to have combined IgE and IgA deficiency. None of these had significant sinusitis, otitis, or other respiratory tract disease (Table II, B). 10 IgA-deficient patients with IgE levels greater than 15 ng/ml had significant respiratory tract disease, while 4 did not. This association between the presence of IgE and respiratory tract disease in IgA-deficient patients was found to be highly statistically significant ($P < 0.0005$). Of the four patients with IgE concentration greater than 15 ng/ml who were free of respiratory disease, three had relatively low IgE levels ranging from 17.5 to 22 ng/ml. The fourth patient had a serum IgE level of 150 ng/ml and had a hookworm infestation.

IgE concentration in patients with ataxia telangiectasia. Serum IgE concentration was determined in 44 patients with ataxia telangiectasia (age range 1.5–43 yr). The geometric mean IgE concentration, 12 ng/ml, differed significantly ($P < 0.001$) from that of the normal population (Table I). Although the mean IgE level for IgA-deficient AT patients was lower than that for non-IgA-deficient AT patients, this difference was not statistically significant. Previous reports have also shown low serum IgE concentrations in patients with AT (7, 21).

The frequency of IgE deficiency and IgA deficiency in patients with ataxia telangiectasia is shown in Table

^aThe term isolated, or selective, IgA deficiency, as used in this report, refers to individuals with serum IgA concentrations of 0.2 mg/ml or less, but with normal concentrations of serum IgG and IgM (20). Thus, individuals with isolated IgA deficiency may or may not be IgE deficient as well.

III. IgA deficiency occurred in 66% of the patients and IgE deficiency in 80%. Combined IgE and IgA deficiency was observed in 25 patients (57%). Although IgA and IgE deficiencies were frequently associated, the correlation was not perfect since 10 IgE-deficient patients (23%) were not IgA deficient, and 4 IgA-deficient patients (9%) were not IgE deficient. Furthermore, it appears that the deficiency of one of the immunoglobulin classes, either IgA or IgE, increases the probability that the other immunoglobulin class will be deficient as well. For example, the frequency of IgA deficiency among IgE-deficient AT patients is 71% while the frequency of IgA deficiency among non-IgE-deficient AT patients is only 44%. Similarly IgE deficiency occurs in 86% of IgA-deficient AT patients but is found in only 67% of AT patients that are not IgA deficient.

Recurrent respiratory tract disease was found in 45% of the AT patients studied. Statistical analysis of the data shown in Table II, C failed to show significant associations between IgE deficiency and respiratory tract disease in patients with AT or in IgA-deficient AT patients. No association was found between IgA deficiency and increased frequency of respiratory tract disease in these patients. ($P > 0.05$).

DISCUSSION

The data for adult serum IgE concentrations, obtained using a double antibody assay, are in good agreement with the observations of other investigators (15, 22). Individuals with IgE values falling below the 10th percentile (15 ng/ml) for the normal population were considered to be IgE deficient. Six of seven individuals with isolated IgE deficiency drawn from our normal adult population were asymptomatic and thus resembled the healthy IgE-deficient individual previously reported (8). The individual with the highest IgE level among the IgE-deficient group had recurrent sinusitis. Since approximately 10% of our normal population was IgE deficient, the finding of an individual with sinusitis and IgE deficiency would not be a rare event even if both conditions were unrelated. It can be concluded that IgE deficiency alone does not usually predispose patients to respiratory tract disease.

Some of our results relating to ataxia telangiectasia appear to differ from those reported by Ammann, Cain, Ishizaka, Hong, and Good (6). These workers measured IgE by reverse cutaneous anaphylaxis and concluded the following: (a) that all patients who were IgA deficient were also IgE deficient, and (b) that all AT patients with combined IgA and IgE deficiency had recurrent sinopulmonary disease. By contrast, our results clearly indicate that although 25 of 44 AT patients had combined IgA and IgE deficiency, 4 AT patients had IgA deficiency but normal IgE levels. This last

TABLE III
Frequency of IgA and IgE Deficiencies in Patients with Ataxia Telangiectasia

| | IgE | | Total |
|----------------------------|----------|----------|-----------|
| | >15 | <15 | |
| | ng/ml | | |
| IgA present (>0.2 mg/ml) | 5 (11%)* | 10 (23%) | 15 (34%) |
| IgA deficient (<0.2 mg/ml) | 4 (9%) | 25 (57%) | 29 (66%) |
| Total | 9 (20%) | 35 (80%) | 44 (100%) |

* The number in the parenthesis is the percentage of the total number of ataxia telangiectasia patients (44) present in each subgroup.

group represented only 9% of our AT patient population and may not have been represented in the smaller patient population studied by Ammann et al. (6).

We have found no association of IgE deficiency with an increased incidence of sinopulmonary disease in AT patients or in IgA-deficient AT patients. This discrepancy may be due to the relatively greater sensitivity of the radioimmunoassay for detection of low normal levels of IgE or the poor correlation between serum IgE concentration and reverse cutaneous anaphylaxis (9) or both.

Depression of delayed hypersensitivity appeared to be the single factor most closely correlated with predisposition to respiratory tract disease in patients with AT, but even this was not statistically significant. Our observations are therefore in general agreement with the conclusions of McFarlin, Strober, Barlow, and Waldmann (23) that predisposition to infection in the AT patient is the result of the combined depression of multiple parts of the immune system and not clearly related to any one single parameter of immune function.

The findings in patients with AT or in individuals with isolated IgE deficiency are in sharp contrast to those observed in patients with isolated IgA deficiency. The latter group showed a highly significant association between chronic respiratory tract disease and the presence of serum IgE. Those individuals with combined IgA and IgE deficiency were, however, uniformly asymptomatic. Our data are in agreement with those of Schwartz and Buckley (9). These authors did not find IgE deficiency frequently associated with predilection to infection in IgA-deficient patients. Further comparison of the present study with that of Schwartz and Buckley (9) is limited by the relative insensitivity of the radioimmunoassay employed in that study as well as the small number of asymptomatic IgA-deficient patients studied.

There are at least two possible explanations for the association of chronic respiratory tract disease with presence of IgE in IgA-deficient patients. First, IgE may play an active role in the pathogenesis of sino-

pulmonary disease in IgA-deficient individuals. One can hypothesize that, in the absence of IgA antibodies, IgE antibodies synthesized locally in the respiratory tract interact with bacterial, viral, and other antigens. Because of the special biologic properties of IgE, this leads to release of histamine and other vasoactive and bronchospastic mediators. The over-all effect is the development of mucosal congestion, increased vascular permeability, and transudation of fluid which would result in a highly favorable environment for growth of microorganisms and destruction of respiratory tract tissues.

Alternatively, the presence or elevation of serum IgE in IgA-deficient patients with chronic respiratory tract disease may be the result of chronic antigenic stimulation of the IgE producing plasma cells in the respiratory mucosa. The infections themselves may be due to as yet undefined immunologic abnormalities in these individuals and not a direct result of the presence of IgE. However, the presence of high levels of IgE locally may further complicate the respiratory tract infections.

From the data presented it would appear that isolated IgE deficiency or the combination of IgE deficiency and IgA deficiency, do not in themselves predispose individuals to respiratory tract disease. In ataxia telangiectasia serum IgE deficiency alone or in combination with IgA deficiency does not correlate well with sinopulmonary disease and the deficiency of no one single immune function can explain the frequent infections seen in these patients. There is a striking association between the presence of IgE and respiratory tract disease in patients with isolated IgA deficiency. It is, however, unclear whether IgE plays a primary role in the pathogenesis of these infections or whether the IgE elevations seen are secondary to as yet undiscovered immunologic abnormalities associated with isolated IgA deficiency.

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