IgE in Immunodeficiency

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In 1966, Ishizaka and co-workers [1,2] identified a unique immunoglobulin, IgE, as the carrier of reaginic antibody activity. Antigenic analysis of this protein, as well as that of two subsequently discovered myeloma proteins, established IgE as an entirely distinct immunoglobulin class.[3–5] The role of IgE in the mediation of immediate hypersensitivity reactions and its association with asthma and other atopic diseases has been well established.[2,6,7] The function of IgE in infectious disease processes and its role in protective immunity is, however, less clearly defined. It is for this reason that many investigators, including ourselves, embarked upon the study of IgE in immunodeficient patients in the hope of assessing the consequences of deficiency of IgE alone or in combination with other deficiencies of humoral and cellular immunity.

Immunoglobulin E exists primarily as monomers composed of two heavy and two light chains linked by covalent disulfide as well as by noncovalent bonds.[8,9] Its molecular weight is approximately 184,500, with the polypeptide portion of the ε heavy chain being 58,500 and the carbohydrate content being approximately 12%.[8,9] IgE is produced by plasma cells in the mucous membranes and regional lymph nodes of the respiratory and gastrointestinal tracts.[10] Autoradiographic studies by Ishizaka *et al* [11] have shown that IgE binds specifically to basophils and tissue mast cells. The interaction of antigen with cell-bound IgE antibody initiates an as yet poorly understood series of reactions which culminate in the degranulation of the basophils and mast cells, and the liberation of histamine, slow reacting substance of anaphylaxis (SRS-A) and the eosinophil chemotactic factor of anaphylaxis (ECF-A).[12] The release of these chemical mediators results in increased vascular permeability, contraction of bronchial smooth muscle, and the influx of

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eosinophils, giving rise to the familiar clinical and pathologic manifestations of immediate hypersensitivity reactions.

Although the role of IgE in protective immunity may be restricted to the mediation of immediate hypersensitivity reactions, one cannot exclude the possibility that IgE antibodies also serve other as yet undefined functions in the maintenance of immunohomeostasis.

Quantitation of IgE

One of the major obstacles to the study of IgE in immunodeficiency diseases has been the difficulty in accurately quantitating this immunoglobulin. Immunoglobulin E is present in nanogram quantities in the serum of normal individuals.[13] The detection and subsequent isolation of two IgE myeloma proteins [4,5] has permitted the development of extremely sensitive radioimmunoassay technics for quantitation of IgE in serum. Johansson, Bennich, and Wide [13] first quantitated serum IgE using a solid phase assay in which specific anti-IgE antibody was bound to Sephadex particles. IgE in serum was quantitated by measuring the inhibition of binding of iodinated-IgE myeloma protein to the Sephadex-bound antibody. A similar type of assay was developed in our laboratory using specific anti-IgE bound to insoluble bromacetylcellulose (BAC) particles.[14] Recently, Gleich and his co-workers [15] described a double antibody radioimmunoassay capable of detecting as little as 1 to 2 ng/ml of IgE in serum. Other methods, such as the radioactive single radial diffusion method of Rowe, have been tried.[16] However, this method is not sensitive enough to detect IgE in the majority of normal adults.[17]

The reverse cutaneous anaphylaxis (RCA) test of Ishizaka and Ishizaka [18] has been used to determine the presence or absence of IgE in immuno-deficient patients.[19–22] If IgE is present, intradermal injection of dilute solutions of anti-IgE antibody will result in the liberation of histamine from skin mast cells, as indicated by a wheal and flare reaction. The concentration of anti-IgE required to elicit such reactions is generally inversely proportional to the patient's serum IgE level; [21] however, the correlation is not perfect.[22] This method is indirect and semiquantitative at best.

In the course of a study of serum IgE levels in immunodeficient patients, using the bromacetylcellulose-bound antibody technic, an unexpectedly large number of patients were found to have normal IgE levels.[14] Low serum IgE levels would have been anticipated on the basis of RCA skin tests in patients with hypogammaglobulinemia and ataxia-telangiectasia.[20–22]

In an attempt to resolve these discrepancies, three different radioimmunoassay methods were used to measure serum IgE in normal individuals and in immunodeficient patients.[23] Sera were studied using: a) the bromacetylcellulose-bound antibody method, b) the Sepharose-bound antibody method of Johansson, Bennich and Wide [13] and c) the double antibody method of Gleich *et al.*[15] To facilitate comparisons, the same specific anti-IgE antibody and the same trace-labeled iodinated IgE myeloma protein were used in all three methods.

Table 1 shows the geometric mean concentrations of IgE in groups of immunodeficient patients and normal adults determined by the three radioimmunoassay procedures. It is clear that the apparent IgE levels for the same group of patients varies considerably with the method of quantitation employed. Paired comparison *t* tests demonstrated that there were significant differences between the IgE values of the same serum measured by the different radioimmunoassays. Generally, the highest values were found using the BAC method, the lowest values were obtained with the double antibody method, and levels determined by the Sepharose method were intermediate. We have found that the three methods agree when serum IgE levels are elevated, as in patients with parasitic disease, but concordance is poor when levels are below 200 ng/ml, as is the case in most immunodeficient patients. Although there is agreement between the IgE values obtained by the

Table 1—Comparison of Geometric Mean Concentrations of IgE in Patients with Ataxia-Telangiectasia, Hypogammaglobulinemia and Schistosomiasis Determined by Different Radioimmunoassay Technics

	Geometric mean (ng/ml)	95% Interval (ng/ml)
Ataxia-telangiectasia (N = 16)		
Double antibody	7	2–27
Sepharose	102	22–472
BAC	120	36–397
Acquired hypogammaglobulinemia (N = 10)		
Double antibody	6	2–17
Sepharose	27	8–91
BAC	87	13–592
Congenital hypogammaglobulinemia (N = 19)		
Double antibody	8	5–14
Sepharose	45	13–156
BAC	199	29–1363
Schistosomiasis (N = 20)		
Double antibody	10,181	1,479–70,048
BAC	11,625	2,388–56,597

BAC and Sepharose methods in patients with ataxia-telangiectasia, this sole example of concordance is not sufficient to insure the validity of either set of measurements. Only the IgE values obtained by the double antibody method are in agreement with what one would expect on the basis of the RCA skin test data. IgE deficiencies detected by the double antibody method are often missed when the BAC or Sepharose methods are used.

Although the specificity of these radioimmunoassays had been previously extensively studied,[23] we undertook further tests of specificity by studying nonprimate animal sera. Kanyerezi and co-workers [24] have observed some degree of antigenic homology between rat and human IgE; however, on the basis of immunochemical and skin test studies by Ishizaka on rabbit, mouse and guinea pig,[25,26] one would not expect extensive cross-reactivity between human IgE and that of nonprimates. The very low or undetectable levels of "human IgE" in nonprimate animal sera, as determined by the double antibody method, are in agreement with these expectations (Table 2). The higher levels of IgE observed in these sera when the BAC and Sepharose methods are used suggest that these methods may be subject to nonspecific inhibition, probably as a result of non-IgE proteins fixing to the BAC or Sepharose particles and sterically inhibiting the binding of radioiodinated IgE to the specific antibody. On the basis of these observations, we believe that the double antibody method is the technic of choice for the measurement of serum IgE.

IgE in Immunodeficiency Diseases

To determine the significance of isolated IgE deficiency and the consequences of the presence or absence of IgE in association with other immune deficits, a number of laboratories, including our own, have undertaken the study of serum IgE levels in apparently normal individuals, as well as in patients with known immunodeficiency diseases.

Table 2—Apparent IgE Concentration (ng/ml) of Various Nonprimate Sera Determined by Double Antibody, Sepharose and BAC Radioimmunoassay

	Double antibody	Sepharose	BAC
Mouse	5.7	69	80
Chicken	9.8	123	64
Goat	4.2	78	400
Sheep	7.6	188	160
Fetal calf	<4	25	30
Bovine	—	—	144

Our own studies were made possible through the cooperation of many investigators who contributed sera and clinical information from patients with a variety of immunodeficiency syndromes.

Using the double antibody radioimmunoassay, the geometric mean concentration of IgE in the serum of 73 normal adults was 105 ng/ml, with a 95% interval from 5 to 2045 ng/ml.[27] These values are very similar to those found by Gleich *et al* [15] and Stites *et al.*[28] Individuals with IgE values falling below the tenth percentile—*ie* less than 15 ng/ml, were considered IgE deficient.

Isolated IgE Deficiency

Two patients with isolated IgE deficiency, on the basis of the reversed cutaneous anaphylaxis test, were described by Hong, Cain and their collaborators.[19,22] Both patients had severe chronic pulmonary disease. These patients were also lymphopenic but had no demonstrable defect in cellular immune function. However, Levy and Chen [29] described a healthy adult with isolated IgE deficiency, and Gleich *et al* [15] described 3 healthy individuals with serum IgE levels less than 6 ng/ml. In a study of healthy adult blood bank donors, we found 7 IgE-deficient individuals (Table 3).[27] All were free from recurrent infections, except 1 woman with sinusitis (Table 4). This individual had the highest IgE level, 12 ng/ml, in the IgE-deficient group. The healthy IgE-deficient individual previously reported by Levy and Chen [29] was found to have a serum IgE concentration of 9 ng/ml by our radioimmunoassay. On the basis of these data, one must conclude that IgE deficiency alone does not usually predispose patients to recurrent or chronic respiratory tract disease.

Table 3—Serum IgE Concentration (ng/ml) in Normal Individuals and Patients with Isolated IgE Deficiency, Isolated IgA Deficiency and Ataxia-Telangiectasia

	No.	Geometric mean	95% interval	% <15
Normal adults	73	105	5-2045	10
Isolated IgE deficiency	7	8	5-14	100
Isolated IgA deficiency	25	35	1-1396	44 (28)*
Ataxia-telangiectasia (total)	44	12	1-122	80
Ataxia-telangiectasia with IgA present	15	19	2-174	66
Ataxia-telangiectasia with IgA deficiency	29	10	1-93	86

* The value in parenthesis is the percentage of IgE deficiency among 18 independently ascertained IgA-deficent individuals

Table 4—Association of Serum IgE Concentration and Respiratory Tract Disease

	Serum IgE		
	>15 ng/ml	<15 ng/ml	P*
Isolated IgE deficiency			
With respiratory tract disease	0	1	
Without respiratory tract disease	0	6	—
Isolated IgA deficiency			
With respiratory tract disease	10	0	
Without respiratory tract disease	4	11	<.0005
Ataxia-telangiectasia			
All patients			
With respiratory tract disease	3	17	
Without respiratory tract disease	6	18	>.22
Patients with IgA deficiency			
With respiratory tract disease	2	14	
Without respiratory tract disease	2	11	>.39

* Fisher exact test; **P** values greater than 0.05 indicate no statistically significant correlation

Ataxia-Telangiectasia

Immunoglobulin E deficiency has been described in patients with ataxia-telangiectasia (AT) and in 65% of their unaffected relatives.[20,30] In their initial study, Ammann *et al*[20] used the RCA test to determine the presence of IgE. On the basis of these tests, there appeared to be a correlation between combined IgA and IgE deficiency and susceptibility to recurrent sinopulmonary disease. However, no correlation between serum IgE level and clinical course was found in a later study by some of the same workers.[30] The serum IgE concentrations of 44 patients with AT were measured in our laboratory by double antibody radioimmunoassay (Table 3).[27] Eighty percent of the patients had serum IgE levels below 15 ng/ml, the geometric mean concentration of IgE being 12 ng/ml. IgE deficiency occurred somewhat more frequently among IgA-deficient AT patients than among non-IgA-deficient patients. As shown in Table 4, there was no correlation between IgE deficiency and susceptibility to respiratory tract disease in patients with AT or in IgA-deficient patients with AT.

All of the IgE-deficient patients with AT reported by Ammann, Hong and co-workers[20,22] were lymphopenic and had variable degrees of deficient cellular immunity. Among patients included in our own study, 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 correlation was not statistically significant. It would, therefore, appear that infection in the patient with AT 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.[31]

Isolated IgA Deficiency and Combined IgE and IgA Deficiency

Mild to moderately severe recurrent respiratory tract infections have been observed in many patients with isolated IgA deficiency.[32] On the other hand, healthy IgA-deficient individuals have also been reported.[33,34] Thus it is not entirely clear why some IgA-deficient individuals are asymptomatic while others suffer recurrent infections. Ammann, Roth and Hong [35] described a mentally retarded child with combined IgA and IgE deficiency and recurrent sinopulmonary infections. However, Schwartz and Buckley [36] did not frequently observe IgE deficiency among patients with IgA deficiency and recurrent respiratory tract disease.

We had the opportunity to study 25 patients with IgA deficiency who did not have any other immunologic deficiency.[27] The geometric mean concentration of IgE in this group was 35 ng/ml, and 11 of the 25 individuals were also IgE deficient (Table 3). None of the 11 individuals with combined IgA and IgE deficiency had significant sinusitis, otitis or other respiratory tract disease (Table 4). Ten of the IgA-deficient patients who were not IgE deficient had significant respiratory tract disease, while 4 were asymptomatic (Table 4). This association between the presence of IgE and respiratory tract disease was found to be highly significant statistically ($P < 0.0005$). Although these data indicate that the combined deficiency of IgA and IgE is not frequently associated with recurrent respiratory tract disease, it does not exclude the possibility that IgE may still play an important role in respiratory tract immunity. In some individuals, other humoral or cellular immune mechanisms may be able to compensate for the deficiency of both IgA and IgE. There was a striking association between the presence of IgE and the occurrence of respiratory tract disease in patients with isolated IgA deficiency. Although many explanations are possible, it seems likely that, in the absence of secretory IgA antibodies, synthesis of IgE may be excessively stimulated by bacterial, viral or other antigens. This lack of modulation by secretory IgA may permit excessively vigorous, immediate hypersensitivity reactions resulting in conditions (*eg*, transudation of fluid, mucosal congestion and broncho-

spasm) highly favorable to the growth of pathogenic microorganisms, as well as for the destruction of respiratory tract tissues.

Immunodeficiency Associated with Hypercatabolism or Excessive Endogenous Immunoglobulin Loss

Immunoglobulin E in patients with immunodeficiency resulting from hypercatabolism or excessive endogenous immunoglobulin loss has been measured by Hong *et al* [22] and Waldmann *et al.*[37] Hong, using the RCA reaction, found IgE present in a patient with protein-losing gastroenteropathy and in 2 patients with hypogammaglobulinemia and lipoid nephrosis. Using the double antibody radioimmunoassay, Waldmann *et al* [37] detected normal serum levels of IgE in patients with intestinal lymphangiectasia, myotonic dystrophy and familial hypercatabolic hypoproteinemia.

Primary Acquired Hypogammaglobulinemia

IgE in patients with acquired hypogammaglobulinemia has been studied by Ishizaka and Newcomb,[21] Stites *et al* [28] and Waldmann *et al.*[37] All three groups of researchers found that IgE was undetectable or markedly depressed in these patients. We have recently extended the original series of acquired hypogammaglobulinemia patients reported by Waldmann [37] to 26 patients. Only 2 of the 26 patients had IgE levels above 15 ng/ml. Both patients had low but detectable serum levels of IgG and IgM and probably represent relatively less severely affected patients than the remainder of the patients in the group with acquired hypogammaglobulinemia (Table 5).

Congenital Hypogammaglobulinemia (X-Linked Infantile and Non-sex-linked Forms)

Study of congenital immunologic deficiency diseases has played an important role in developing our understanding of lymphoid system

Table 5—Serum IgE Concentration (ng/ml) in Normal Individuals and in Patients with Congenital and Acquired Hypogammaglobulinemia

	No.	Geometric mean	95% Interval	% <15
Normal adults	73	105	5–2045	10
Acquired hypogammaglobulinemia	26	6	1–32	92
Congenital hypogammaglobulinemia (total)	25	9	5–16	96
Congenital hypogammaglobulinemia (sex-linked)	11	9	6–14	100
Congenital hypogammaglobulinemia (non-sex-linked)	14	9	4–18	93

ontogeny and the development of normal immunologic processes. Clinical and laboratory investigations of these patients have not only yielded important information but also have stimulated and directed basic research into the development of immunologic functions. Therefore, the study of IgE in patients with congenital immunodeficiency states might give us some insight into the ontogeny of the immunoglobulin E system, as well as help define its relationship to the thymic and bursal components of the immune system.

Newcomb and Ishizaka [21] and Hong *et al* [22] failed to detect IgE in the skin of patients with congenital hypogammaglobulinemia. Serum IgE levels less than 20 ng/ml were detected in 3 patients with infantile sex-linked hypogammaglobulinemia by Hong *et al* [22] and in 1 similar patient by Stites *et al.*[28] Twenty-five patients with congenital hypogammaglobulinemia (with intact cellular immunity) have been studied in our laboratory using the double antibody radioimmunoassay. Twenty-four of the 25 patients were IgE deficient—*ie*, with levels less than 15 ng/ml (Table 5). The IgE levels of patients with infantile sex-linked hypogammaglobulinemia (Bruton) were similar to those of patients with familial non-sex-linked and sporadic hypogammaglobulinemia.

DiGeorge Syndrome and Severe Combined Immunodeficiency Syndrome

We have studied 1 patient with the DiGeorge syndrome. Serum IgE was easily detectable in this child at 7 and 17 months; IgE was elevated on both occasions (Table 6).

Deficiency of IgE has been observed previously in 2 patients with combined immunodeficiency syndrome.[22,28] A study of 8 such patients in our laboratory revealed unexpected heterogeneity within this group (Table 6). Two patients were IgE deficient, while low normal values

Table 6—Serum IgE Concentration (ng/ml) in Patients with DiGeorge Syndrome and Combined Immunodeficiency Syndrome

Patient	Age (mos)	IgE	Diagnosis
DG	7	795	DiGeorge syndrome
DG	17	578	DiGeorge syndrome
JS	8	8	Combined immunodeficiency syndrome
SS	12	8	Combined immunodeficiency syndrome, sex-linked
JB	5	22	Combined immunodeficiency syndrome, autosomal recessive
KS	11	18	Combined immunodeficiency syndrome, sex-linked
GF	6	17	Combined immunodeficiency syndrome
JOB	7	306	Combined immunodeficiency syndrome, sex-linked
JAB	8	991	Combined immunodeficiency syndrome, sex-linked

were observed in 3 others. Two brothers, JAB, and JOB, had elevated levels of serum IgE. The combined immunodeficiency disease in these 2 infants was characterized by sex-linked inheritance, absence of delayed hypersensitivity reactions and the transient presence of IgM between the fourth and sixth months of life, but an absence of IgG and IgA. Both infants had dysplastic thymuses lacking Hassall's corpuscles and corticomedullary differentiation; their lymph nodes lacked germinal centers as well as paracortical lymphocytes. JOB failed to respond to phytohemaglutinin but consistently reacted normally to allogeneic cells *in vitro*. JAB had died 4 years earlier and had not been tested with PHA or allogeneic cells.

The persistence of IgE in some patients with combined immunodeficiencies suggests that IgE may arise relatively early in immunologic ontogeny. This idea gains some support from physicochemical studies on the IgE myeloma protein, PS,[9] which suggest that IgE is more closely related to the IgM monomer than to IgA or IgG. However, at this point, this hypothesis represents unfettered speculation and indicates that further investigations into the ontogeny and phylogeny of the IgE system are definitely required.

The observation of elevated IgE levels in 1 patient with the DiGeorge syndrome and in 2 brothers with an unusual form of combined immunodeficiency raise some interesting questions concerning the control of IgE synthesis in man. Tada and his coworkers [38,39] have found that x-irradiation, thymectomy, splenectomy or treatment with antilymphocyte serum result in an accentuation and prolongation of the homocytotropic (IgE) antibody response in adult rats. These authors suggest that these procedures result in the depletion of a thymic-dependent lymphocyte (T-cell) pool whose function is to limit the synthesis of homocytotropic antibody. In addition, suppression of homocytotropic antibody synthesis has been observed after the passive administration of specific IgG antibody.[40,41] Patients with DiGeorge syndrome and combined immunodeficiency that synthesized elevated levels of IgE had T-cell deficiencies but had at least some bursal-dependent cell functions remaining. Elevated IgE levels in these patients may have been the result of the absence of these IgE-modulating T-cells hypothesized by Tada.[41] Alternatively, these patients were probably also unable to synthesize the specific IgG antibodies required to suppress homocytotropic antibody synthesis. Similar mechanisms may also be involved in the hypergammaglobulinemia E observed in 2 patients with recurrent infections, subnormal antibody formation and impaired cellular immunity reported by Buckley.[42]

Conclusions

The quantitation of serum IgE has been one of the major problems in the study of IgE in immunodeficient patients. Spuriously high IgE levels have been observed in immunodeficient patients when solid phase radioimmunoassay technics were employed. We have presented data that indicate that the double antibody radioimmunoassay is the method of choice for the measurement of serum IgE.

Thirteen individuals with isolated IgE deficiency have been reported. Two patients, who were lymphopenic as well as IgE deficient, had recurrent sinopulmonary disease, another individual had minor difficulties with sinusitis but the remaining 10 individuals with isolated IgE deficiency were asymptomatic. We have studied 11 individuals with combined IgA and IgE deficiency, and all were free from respiratory tract disease. It must be concluded, therefore, that isolated IgE deficiency or combined IgA and IgE deficiency do not, in themselves, predispose individuals to recurrent respiratory tract disease.

Respiratory tract disease was, however, observed in 10 of 14 IgA-deficient patients who had normal or elevated levels of serum IgE. These findings suggest that immediate hypersensitivity reactions may play an important role in the pathogenesis of respiratory tract disease in some patients with defective IgA secretory immunity.

IgE deficiency has been found in patients with ataxia-telangiectasia. In our own series, 80% of the patients with AT were IgE deficient. No significant correlation between IgE deficiency or combined IgE and IgA deficiency and susceptibility to respiratory tract disease was found in these patients with AT.

In general, reduced levels of serum IgE are seen in patients with a generalized defect in immunoglobulin synthesis. Absence or marked reduction of serum IgE levels were observed in patients with congenital hypogammaglobulinemia, primary acquired hypogammaglobulinemia and hypogammaglobulinemia associated with thymoma. In contrast, normal IgE levels have been observed in patients with hypogammaglobulinemia resulting from hypercatabolism (familial hypercatabolic hypoproteinemia, myotonic dystrophy) or from excessive endogenous loss (intestinal lymphangiectasia, protein-losing gastroenteropathy, nephrosis).

An elevated level of serum IgE was found in a patient with the DiGeorge syndrome. The presence of IgE in the DiGeorge syndrome and the absence of IgE in patients with congenital hypogammaglobulinemia are consistent with the concept that the IgE system is part of the bursal-dependent portion of the lymphoid immune system.

Unexpected heterogeneity was found among patients with severe combined immunodeficiency. IgE was low or absent in most of these patients, but elevated IgE levels were observed in 2 brothers with an unusual form of combined immunodeficiency syndrome. One may speculate that the persistence of IgE in some patients with combined immunodeficiencies suggests that this immunoglobulin may arise relatively early in immunologic ontogeny.

There is very little information available concerning IgE in patients with various dysgammaglobulinemias other than isolated IgA deficiency. Clearly, additional studies of IgE in immunodeficient patients, especially in patients with DiGeorge syndrome, combined immunodeficiency syndrome and various dysgammaglobulinemias, are needed.

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