

Clinical manifestations of IgE hypogammaglobulinemia

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Background: Although IgE has been shown to play a role in the expulsion of intestinal parasites in experimental animals, its overall contribution to host defense in humans remains a subject of controversy. In order to clarify the potential role of IgE in host defense, we have studied the clinical characteristics of patients with serum IgE levels of <2.5 IU/mL, using patients with normal or elevated IgE levels as controls.

Objective: To determine the clinical characteristics of IgE deficiency.

Methods: Serum IgE levels were measured in 420 adult patients seen in our Allergy-Immunology Clinic over a period extending from January, 1990 to March, 1996. All subjects were examined by one of the authors (JKS or GHK) using a standardized history and physical examination form. Patients with IgE levels of <2.5 IU/mL also had measurements of serum IgG, IgG subclasses, IgA and IgM. All IgE-deficient patients and 73% of those with normal to elevated IgE levels underwent RAST and/or skin testing for Type I hypersensitivity, and, where clinically indicated, had serum drawn for autoimmune serologic profiles. Infectious complications were documented by culture. The American Rheumatology Association criteria were used to establish a diagnosis of autoimmune disease.

Results: Forty-four patients were found to have IgE levels of <2.5 IU/mL; 57% of these had depressed serum levels of other immunoglobulins, and 43% had isolated IgE deficiencies. Respiratory symptoms were equally common in IgE-deficient patients and in patients with normal to elevated IgE levels. IgE-deficient patients, however, were more likely to complain of arthralgias ($P < .0001$), chronic fatigue ($P < .0001$), and symptoms suggestive of airway infection ($P = .0119$). Compared with controls, patients with IgE deficiency had a higher prevalence of autoimmune disease (46% versus 15%) ($P < .0001$) and nonallergic reactive airway disease (73% versus 20%) ($P < .0001$). There was no difference in the prevalence of these diseases in patients with selective IgE deficiency as compared with those with IgE deficiency complicated by deficits in other immunoglobulin classes. IgE-deficient patients with multiple immunoglobulin deficiencies, however, were more likely to have serious infection involving both the upper and lower respiratory tract than those with isolated IgE deficiency.

Conclusions: IgE-deficient patients have an increased prevalence of multiple immunoglobulin deficits, autoimmune disease, and nonallergic reactive airway disease when compared with a clinic population of patients with normal to elevated IgE levels.

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INTRODUCTION

Although IgE antibody has been shown to play a role in the expulsion of

intestinal parasites in experimental animals,¹ its overall contribution to host defense in humans remains a sub-

ject of controversy. Cain et al reported a case of IgE deficiency associated with chronic sinopulmonary disease, and postulated that IgE protects the mucosal barrier against infection.² In contrast, Levy and Chen reported a 28-year-old woman with isolated IgE deficiency unassociated with clinical evidence of disease, and claimed that IgE is not essential for the prevention of sinopulmonary infection.³ Both of these studies used reversed passive anaphylaxis rather than in vitro serum assays to measure IgE. Using a radioimmunoassay, Polmar et al found no evidence of respiratory tract disease in six of seven adults with IgE levels falling below the 10th percentile (15 ng/mL).⁴ In response to some of these disparate reports, Ammann and Good noted that isolated immunoglobulin deficiencies do not always result in clinically evident disease, and that reports of apparently healthy IgE-deficient persons do not preclude a protective role for this immunoglobulin class.⁵ Low serum levels of IgE often accompany other immunologic deficiency diseases, including ataxia telangiectasia, Bruton's hypogammaglobulinemia, common variable immunodeficiency, and IgG subclass deficiencies,^{4,6} but the contribution of IgE hypogammaglobulinemia to impaired host defenses in these cases is unclear.

The most compelling evidence supporting a protective role for IgE in humans was reported by Schoettler et al.⁷ They examined the sera of 23 family members of 58-year-old nonidentical twins with chronic bronchitis, fibrotic lung disease, and low serum IgE levels. Twelve of the kindred were IgE deficient (serum levels <5 IU/mL) and had chronic sinopulmonary disease. Serum levels of IgG, IgG subclasses, IgA and IgM, and antibody responses

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to tetanus toxoid and Hemophilus influenzae type b were normal in all but three of these subjects. Importantly, serum IgE levels were normal (>10 IU/mL) in nine asymptomatic relatives. IgE deficiency appeared to be inherited as an autosomal dominant, with a variable degree of penetrance.

We report the clinical characteristics of 44 adult (≥ 18 years old) patients with low levels of serum IgE (<2.5 IU/mL) seen in our Immunology-Allergy Clinic from 1990 to 1996, 19 of whom had isolated IgE deficiency and 25 of whom had associated deficiencies in other immunoglobulin classes. We compare the findings with those of 376 patients with normal to elevated IgE levels seen in our clinic over the same period of time.

METHODS

Subjects

The study was performed on 420 randomly selected adult patients seen in our Allergy-Immunology Clinic over a period extending from January, 1990 to March, 1996. Subjects had been examined by one of the authors (JKS or GK), using a standardized history and physical examination form, and represent the great majority of patients seen by the examiners over this period of time. For the purposes of this study, IgE deficiency is defined as an IgE level of <2.5 IU/mL.

Serum IgE levels were performed on all subjects. Those with IgE levels of <2.5 IU/mL also had measurements of serum IgG, IgG subclasses, IgA and IgM, and a repeat IgE measurement to confirm the deficiency. All IgE-deficient patients and 73% of patients with normal or elevated IgE levels underwent RAST testing and/or skin testing for Type I hypersensitivity, and where clinically indicated, had serum drawn for autoimmune serologic profiles. Because IgE levels may not stabilize until age 15, only patients ≥ 18 years of age were selected for study.

Standard criteria were used to establish a diagnosis of allergic and vasomotor rhinosinusitis, chronic bronchitis, and extrinsic and intrinsic

asthma.^{8,9} Infectious causes of upper and lower airway disease were documented by culture. The American Rheumatology Association criteria were used to establish diagnoses of autoimmune and rheumatoid diseases.¹⁰

Immunoglobulin and RAST Assays

Total serum IgE was measured using a Phadebas IgE paper radioimmunosorbent test (PRIST) (Kabi Pharmacia Diagnostics AB, Uppsala Sweden). The detection range of this test is $0.5 \geq 800$ kU IgE/L.

Serum levels of IgE antibody to 60 regional seasonal and nonseasonal allergens was measured using a Phadebas radioallergosorbent test (RAST) (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden).

Serum levels of IgG, IgA, and IgM were measured by single radial immunodiffusion using Kallestad quantiplate/Endoplate test kits (Sanofi Diagnostics Pasteur, Inc, Chaska, MN). Serum IgG subclasses were measured by single radial immunodiffusion using ICN kits (ICN Biomedicals, Irvine, CA).

Skin Testing

Epicutaneous and, where indicated, intradermal skin tests were done using 66 regional seasonal and nonseasonal antigens (Miles Inc, Spokane, WA).

Statistical Analysis

Statistical analysis was done using StatMost (DataMost Corporation, Salt Lake City, Utah). Probability testing was done by Chi square analysis and 2-tailed Student's *t* test. Most percentages have been rounded off to the nearest whole number to improve readability.

RESULTS

Forty-four (10.5%) of the 420 patients studied were found to have serum IgE levels of <2.5 IU/mL. The IgE hypogammaglobulinemic group included 37 women and 7 men with a mean age of 45 ± 13.9 (SD). Three hundred seventy-six patients had normal to elevated IgE levels. This group included 280 women and 96 men with a mean age of 43.8 ± 15.8 (SD), and hence-

forth will be referred to as the control group.

Presenting Symptoms

On presentation, respiratory symptoms suggestive of reactive airway disease (clear rhinorrhea, nasal congestion, nonproductive cough, and/or wheezing) were present in 73% of IgE-deficient patients, and in 71% of patients with normal to elevated IgE levels ($P = .8716$) (Table 1). Respiratory symptoms suggestive of infection (purulent rhinorrhea, purulent sputum production) were present in 11% of IgE-deficient persons (83% of whom also had reactive airway symptoms) and in 3% of control patients ($P = .0119$). The majority of patients in both study groups were seen in our clinic because of these respiratory symptoms, which were considered to be allergic in origin by most patients.

Musculoskeletal symptoms were present in 43% of IgE-deficient patients and in 14% of controls ($P < .0001$). Whereas the incidence of myalgias was similar in the two groups, IgE-deficient patients had a higher incidence of polyarthralgias than controls ($P < .0001$). In addition, chronic fatigue as a major symptom was present in 30% of IgE-deficient patients as compared with 4% of controls ($P < .0001$). There was no significant difference in other miscellaneous symptoms between the two study groups. Complaints of skin eruptions and pruritus were also similar in the two study groups.

Diagnostic Findings

All patients with IgE hypogammaglobulinemia had negative RAST and/or skin tests. Fifty-three percent of patients with normal to elevated IgE levels tested positive, and 20% tested negative to the same allergen panels. Twenty-seven percent of controls were not RAST or skin tested because of a lack of clinical indications.

Forty-three percent of the 44 IgE-deficient patients had isolated decreases in IgE, whereas 57% had depressed serum levels of other immunoglobulins—thirteen with isolated

Table 1. Comparison of Presenting Symptoms of Patients with Low versus Normal to High Serum IgE Levels

Presenting Symptoms	Low IgE Patients* (N = 44)	Control Patients† (N = 376)	P‡
Respiratory	80%	74%	.5083
“Reactive”§	73%	71%	.8716
“Infective”	7%	3%	.0119
Cutaneous¶	11%	11%	.8304
Musculoskeletal	43%	14%	<.0001
Polyarthralgias	32%	7%	<.0001
Myalgias	11%	7%	.4907
General			
Chronic fatigue	30%	4%	<.0001
Miscellaneous	11%	6%	.2402

* Serum IgE <2.5 IU/ml.

† Serum IgE normal to high.

‡ Chi-square.

§ Nasal congestion, clear rhinorrhea, nonproductive cough, and/or wheezing.

|| Purulent rhinorrhea and/or purulent sputum production.

¶ Skin eruption and/or pruritus.

IgG subclass deficiencies, six with IgG deficiency, three with IgA deficiency, one with combined IgG and IgA deficiency, one with IgA and IgG subclass deficiency, and one with IgM deficiency. In descending order, subclass deficiencies (including those associated with IgG deficiency) were most commonly seen in IgG4 (N = 12), IgG1 (N = 5), IgG3 (N = 3), and IgG2 (N = 2).

The isolated IgE deficiency group included 17 women and 2 men with a mean age of 43.7 ± 14.5 (SD). The multiple immunoglobulin deficiency group included 20 women and 5 men with a mean age of 46 ± 13.7 (SD).

Reactive Airway Disease

Nonallergic reactive airway disease was present in 73% of the 44 IgE-deficient patients, and in 20% of the 376 controls ($P < .0001$) (Table 2). In contrast, allergic (IgE-mediated) airway disease was documented in 53% of controls and in none of the IgE-deficient patients ($P < .0001$). There was no significant difference in the prevalence or nature of reactive airway disease in patients with isolated IgE deficiencies when compared with those with multiple immunoglobulin deficiencies.

Diagnoses in the 44 IgE-deficient patients included rhinitis (68%), sinusitis (61%), bronchitis (46%), and asthma (23%) (Fig 1). The incidence of bronchitis and asthma in non-smokers was 34% and 18%, respectively. Both upper and lower airways were involved in 46% of patients.

Nonallergic rhinitis was present in 20%, sinusitis in 5%, bronchitis in 4%, and asthma in 3% of patients with normal to elevated IgE levels. Both the upper and lower airways were involved in 4% of these patients.

Autoimmunity

Forty-six percent of the 44 IgE-deficient patients and 15% of the 376 pa-

tients with normal to elevated IgE levels had clinical findings of autoimmune disease ($P < .0001$) (Table 2). Compared with controls, the incidence was significantly higher both in patients with isolated IgE deficiency ($P = .0007$) as well as in patients with multiple immunoglobulin deficiencies ($P = .0005$).

Diagnoses in the 44 patients with IgE deficiency included: primary myxedema (N = 6), rheumatoid arthritis (N = 5), Sjögren's syndrome (N = 4), Raynaud's (N = 3), systemic lupus erythematosus (N = 2) and pernicious anemia, autoimmune neutropenia, anticardiolipin antibody syndrome, autoimmune thyroiditis, ulcerative colitis, Crohn's disease, Guillain-Barre syndrome, sprue, and Behcet's syndrome (N = 1 each). Eight of these patients had two or more autoimmune diseases (Fig 2).

Diagnoses in patients with normal to high IgE levels included primary myxedema (N = 25), Sjögren's syndrome (N = 11), rheumatoid arthritis (N = 10), systemic lupus erythematosus (N = 4), anticardiolipin antibody syndrome (N = 2), Graves disease (N = 2), and autoimmune polyneuropathy, polymyalgia rheumatica, autoimmune thyroiditis, and juvenile rheumatoid arthritis (N = 1 each). Only two of these patients had two or more autoimmune diseases ($P < .0001$ as compared with the IgE deficiency group).

Infection

Documented bacterial airway infection occurred in 21% of patients with iso-

Table 2. Comparison of Diagnoses in Patients with Isolated IgE Deficiency, IgE Plus Other Immunoglobulin Deficiencies, and Normal to High IgE Levels

Study Group	Autoimmune Disease	Nonallergic Reactive Airway Disease
1. Low IgE patients (N = 44)	46%	73%
a. Isolated decrease (N = 19)	47%	68%
b. Multiple Ig deficiency (N = 25)	44%	76%
2. Normal to high IgE patients (N = 376)	15%	20%
P*		
1 vs 2	<.0001	<.0001
1a vs 1b	.9336	.8279
1a vs 2	.0007	<.0001
1b vs 2	.0005	<.0001

* Chi-square.

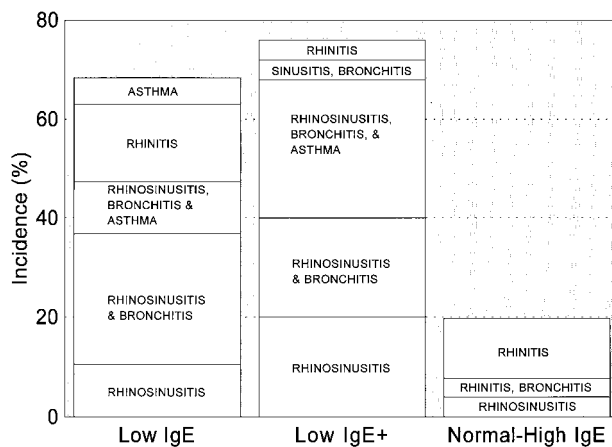


Figure 1. Comparative prevalence of nonallergic reactive airway disease in patients with low IgE levels and patients with normal to high IgE levels. Reactive airway disease occurred in 68% of patients with isolated decreases in IgE (low IgE) (N = 19), 76% of those with multiple immunoglobulin deficiencies (low IgE+) (N = 25), and in 20% of patients with normal to high IgE levels (N = 376). The difference in the prevalence of nonallergic airway disease in IgE deficient patients and patients with normal to elevated IgE levels is highly significant ($P < .0001$).

lated IgE deficiency (Fig 3). In two cases, infections were restricted to the sinuses, and were recurrent. One patient had recurrent pneumonia, and one had sinusitis and bronchitis. In comparison, 32% of the 25 patients with multiple immunoglobulin deficiencies

had documented bacterial airway infections ($P > .05$). These patients were more likely to have multiple sites of infection involving both the upper and lower respiratory tract than those with isolated decreases in IgE. In addition, their infections were more severe and

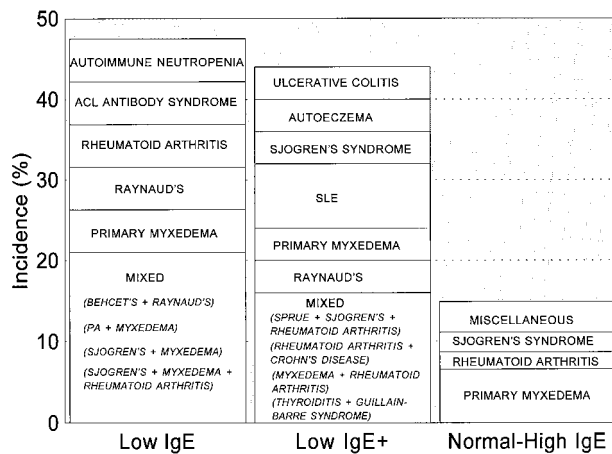


Figure 2. Comparative prevalence of autoimmune disease in patients with low IgE levels and patients with normal to high IgE levels. Autoimmune disease occurred in 47% of patients with isolated decreases in IgE (low IgE) (N = 19), 44% of those with IgE deficiency associated with decreases in other immunoglobulin classes (low IgE+) (N = 25), and in 15% of patients with normal or high IgE levels (N = 376). The difference in the prevalence of autoimmune disease in patients with IgE deficiency and those with normal to elevated IgE levels is highly significant ($P \leq .0007$). Miscellaneous diagnoses in patients with normal to high IgE levels include systemic lupus erythematosus (1.1%), anticardiolipin antibody syndrome (0.5%), Graves' disease (0.5%), two patients with several autoimmune diseases (rheumatoid arthritis and Sjögren's; rheumatoid arthritis, Sjögren's and autoimmune thyroiditis) (0.5%), and autoimmune polyneuropathy, polymyalgia rheumatica, and juvenile rheumatoid arthritis (0.3% each).

occurred more frequently than those seen in the isolated IgE deficiency group. In both groups, the most commonly isolated pathogens were (in descending order) *Hemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.

Four (9%) of the 44 patients with IgE deficiency had chronic viral infections—two with the Epstein-Barr virus, and one each with varicella zoster and hepatitis C. The incidence of persistent viral infections in the control group is not known.

DISCUSSION

The finding of multiple immunoglobulin deficiencies in nearly sixty percent of our IgE deficient patients is in keeping with previous reports linking IgE deficiency with other immunologic deficiency states.^{4,6} In addition to IgE, immunoglobulin deficiencies occurred in IgG subclasses (56%), IgG (28%), IgA (20%), and IgM (4%) in our series. IgG4 accounted for the majority of subclass deficiencies, followed by IgG1, IgG3, and IgG2. Since the heavy chains for immunoglobulins are coded on chromosome 14, with IgA1, IgG2, IgG4, IgE, and IgA2, in sequential order,¹¹ linkage of these may explain the particularly high incidence of IgG4 and IgA deficiencies in our IgE hypogammaglobulinemic patients.

Patients with multiple immunoglobulin class or subclass deficiencies may have frequent infections involving, in particular, the respiratory tract. Hence, our findings that IgE-deficient patients were more likely than the controls to present with symptoms suggestive of airway infection, and that the extent and severity of airway infection was greatest in the IgE-deficient patients with multiple immunoglobulin deficiencies is not unexpected. It remains unclear, however, as to whether IgE deficiency itself contributed to an increased susceptibility to bacterial infection.

In keeping with the report of Schoettler and associates,⁷ we documented a high incidence of respiratory disease in our IgE hypogammaglobulinemic pa-

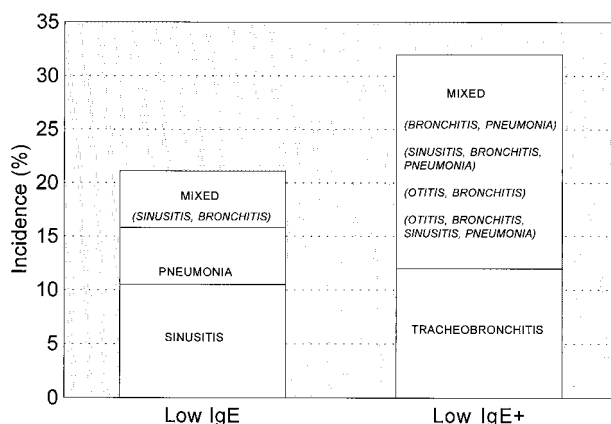


Figure 3. Comparative prevalence of bacterial airway infections in patients with isolated IgE deficiency (low IgE) (N = 19) and IgE deficiency associated with decreases in other immunoglobulin classes (low IgE+) (N = 25). Documented infection occurred in 21% of the low IgE group and in 32% of the low IgE+ group ($P > .05$). Multiple severe infections involving both the upper and lower airways were more common in the mixed immunoglobulin deficiency group. The most commonly isolated pathogens were *Hemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.

tients. The clinical findings were those of nonallergic reactive airway disease involving predominantly the upper airway or both the upper and lower airways. These findings are in keeping with the possibility that IgE is an important part of the mucosal defense system; however, the prevalence of symptomatic airway disease in our IgE-deficient patients was nearly identical to that found in our patients with normal to elevated IgE levels, respiratory symptoms providing the main reason for patients in both study groups having sought medical care in our clinic. The finding of a high prevalence of respiratory disease in our IgE-deficient patients may reflect selection bias inherent in our allergy practice. Only further studies involving a randomly selected population will resolve this issue.

Perhaps the most striking finding in this study is the unexpectedly high prevalence of autoimmune disease in IgE-deficient patients. This propensity to develop autoimmune disease was not dependent on the presence of associated immunoglobulin deficits, autoimmune disease being as common in patients with selective IgE hypogammaglobulinemia as in the multiple immunoglobulin deficiency group of pa-

tients. In addition, the finding did not appear to result from a selection bias inherent in our practice, since we do not have a rheumatology practice, and since the prevalence of autoimmune disease was significantly lower in the patient group with normal to elevated IgE levels. Furthermore, although IgE-deficient patients were more likely to complain of polyarthralgias than patients with normal to elevated IgE levels, they were seen in our clinic because of suspected respiratory allergies or recurrent airway infection, and not because of their musculoskeletal symptoms.

Our finding of an increased prevalence of autoimmune disease in patients with IgE deficiency is in keeping with reports linking deficiencies in other immunoglobulin classes with autoimmune disease.^{12,13} Patients with selective IgA deficiency have an unusually high prevalence of autoimmune diseases similar to those seen in our patients with IgE hypogammaglobulinemia, including rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroiditis, Sjögren's syndrome, and pernicious anemia.^{12,13} It has been postulated that IgA may protect against autoimmunization by preventing the systemic absorption of mu-

cosal antigens. As noted by Liblau and Bach,¹³ a lack of antigen exclusion at the mucosal barrier could allow exogenous antigens to induce autoimmune responses by stimulating autoreactive lymphocytes through molecular mimicry¹⁴; by promoting immune complex formation¹⁵; by superantigen-induced polyclonal activation of lymphocytes¹⁶; by inducing a perturbation of the idiotypic network¹⁷; and/or by aberrant induction of MHC class II antigens.^{18,19} A lack of protection against penetration of the mucosal barrier by infectious agents having the potential to trigger autoimmune disease is another possibility.¹² Shared genetic factors that predispose to both immunoglobulin deficiency and to autoimmune phenomena is another possible explanation for the association of selective IgA deficiency and autoimmune disease.^{12,13} In blood donors, selective IgA deficiency is associated with the same MHC alleles and haplotypes that appear to predispose to several autoimmune diseases, notably the HLA-A1, B8, DR3 haplotype, and the C4 null allele.¹³ The finding of a similar tendency in IgE-deficient patients to develop autoimmune disease suggests that IgE, like IgA, may protect against autoimmune reactivity by promoting the mucosal exclusion of exogenous antigens, and/or by being associated with common genetic factors that predispose to both IgE deficiency and autoimmunity.

The confirmation of the association of isolated IgE deficiency and autoimmunity will depend on additional studies demonstrating an increased prevalence of selective IgE deficiency in a population of patients with autoimmune disease as compared to healthy controls.

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