Familial IgE Deficiency Associated with Sinopulmonary Disease*

Joyce J. Schoettler, M.D.;† Leo A. Schleissner, M.D., F.C.C.P.;‡ and Douglas C. Heiner, M.D., Ph.D.§

Three generations of relatives of 58-year-old nonidentical twins with chronic bronchitis and fibrotic lung disease were evaluated. Sera of 23 family members, 14 with a history of excessive sinopulmonary infections, were examined for deficiencies of immunoglobulin classes, IgG subclasses, and specific antibody to tetanus toxoid and Hemophilus influenzae type b. Of 14 symptomatic family members, 12 had serum IgE concentrations <5 IU/ml. Four had values <1 IU/ml. Serum IgE was >10 IU/ml in all nine asymptomatic individuals. Inheritance of low IgE appeared to be autosomal dominant, with variable penetrance. IgA was low normal (70-90 mg/dl) in three individuals. Two of these were IgE deficient. One symptomatic child had unmeasurable IgG2 (<10 mg/dl) and IgE (<0.5 IU/ml). This kindred demonstrates that IgE deficiency can be familial, and associated with sinopulmonary disease.

*(Chest 1989; 96:516-21)*

IgE deficiency may occur in individuals with an otherwise normal immunologic profile, without evidence of illness.1 However, there have been occasional reports relating low or absent serum IgE to recurrent infection.24 Low serum concentrations of IgE often accompany other immunoglobulin deficiencies, as in X-linked hypogammaglobulinemia, common variable immunodeficiency, and severe combined immune deficiency.24 Individuals suffering from ataxiatelangiectasia, a progressive neurologic syndrome, often suffer recurrent sinopulmonary infections in association with deficient IgG2, IgG4, IgE, or a combination of these.3,8,10 The present study describes three generations of a family affected by an unusual frequency of sinopulmonary infection in association with IgE deficiency.

CASE REPORTS

CASE 1

The index patient was a 58-year-old Caucasian woman who presented to her physician (L.S.) with a long history of paroxysmal dry, painful cough, shortness of breath on exertion, and occasional hemoptysis. There was no history of cigarette smoking. She had been hospitalized several times with pneumonia involving various areas of each lung. The right upper lobes and superior segments of the lower lobes were at times involved, possibly due to aspiration of vomitus induced by cough. Acute pulmonary infiltrates resolved with antibiotic therapy in each instance.

*From Harbor-UCLA Medical Center, Torrance, California.
Presented at the Annual Meeting, American College of Allergists, Boston, November 15, 1987; (Ann Allergy 60:157, 1988 [abstract]).
Supported in part by National Institutes of Health Training Grant 5 T32 HD07245-06.
†Adjunct Instructor of Pediatrics, Division of Allergy and Immunology.
‡Clinical Associate Professor of Medicine.
§Professor of Pediatrics, UCLA School of Medicine.
Manuscript received July 11, 1988; revision accepted January 1, 1989.
Reprint requests: Dr. Schoettler, Allergy and Clinical Immunology, Children's Hospital, 4650 Sunset Blvd, Los Angeles 90027

Bronchiectasis was confirmed by bronchogram. Repeated sputum cultures were without growth of pathogenic organisms, except for *Hemophilus influenzae* on one occasion, and *Citrobacter* on another. Cultures from bronchoscopy and bronchoalveolar lavage (BAL) were also negative, although BAL fluid contained many white cells, predominantly neutrophils.

Pulmonary function tests showed evidence of both restrictive and obstructive lung disease, with progression of the restrictive component over time (Table 1). Gallium-67 scanning resulted in diffuse increased uptake over both lung fields in 1981 and 1986. The patient underwent bronchoscopy on two occasions; inflamed bronchial mucosa and yellow adherent material in the bronchial lumen were noted each time. A transbronchial biopsy in 1981 confirmed the presence of focal emphysema and bronchitis, plus chronic interstitial inflammation and fibrosis (Fig 2). On light microscopy, collections of neutrophils were found in luminal secretions and in bronchial washings.

Arterial blood gas measurements at rest are consistently normal. In a recent incremental exercise test, the patient demonstrated exercise-induced hypoxemia, typical of restrictive lung disease. She stopped exercise at 15 watts because of dyspnea. Arterial O₂ saturation (measured by ear oximetry) decreased from 98 percent at rest to 92 percent during exercise. In a subsequent test, performed while breathing 100 percent O₂, saturation remained near 100 percent.

Serum alpha-antitrypsin, antitrypsin converting enzyme, and alpha fetoprotein were normal. Serologic studies included antinuclear antibody positive at a titer of 1:320 (speckled pattern), but a normal titer of antibodies to dsDNA, and absence of Sm, Ro, La, centromere, and mitochondrial antibodies. Rheumatoid factor was not present. Total hemolytic complement, C3, and C4 were normal. The patient was anergic, as evidenced by absence of delayed skin hypersensitivity to PPD, Coccidioides sp, Histoplasma sp, Aspergillus sp, Candida sp, and eight antigens on the Multitest CMI (Merieux Institute, Inc, Miami, FL).

Further immunologic evaluation included quantitation of immunoglobulin classes and subclasses. The serum IgM concentration was 142 mg/dl, IgA 155 mg/dl, and IgG 540 mg/dl. The IgG1 serum level was 426 mg/dl, IgG2 173 mg/dl, IgG3 60 mg/dl, and IgG4 10 mg/dl. All values are normal for age. IgG being low normal due to borderline low IgG1, IgG2, and IgG4. However, serum IgE was markedly decreased, ranging from <0.5 to 0.8 IU/ml over several months of study.

Antigen-specific antibody formation was evaluated by measurement of serum IgG antibodies to *H influenzae* type b capsular antigen (PRP) and tetanus toxoid. Serum samples were obtained before and one month after immunization with PRP and tetanus to assess the expected booster response. Her normal responses suggested intact functional antibody production for both carbohydrates and protein antigens.

Evaluation of cellular immunity demonstrated normal quantities of granulocytes, T and B lymphocytes, and T-cell subsets. There was a normal T4:T8 ratio of 2.4. Lymphocyte proliferation responses to phytohemagglutinin, concanavalin A, and pokeweed mitogen were normal.

**Table 1—Pulmonary Function of Case 1, Over a 6-Year Period**

<table>
<thead>
<tr>
<th>Date</th>
<th>7/81</th>
<th>5/86</th>
<th>9/87</th>
<th>11/87</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (L)</td>
<td>2.27</td>
<td>1.8</td>
<td>1.59</td>
<td>1.47</td>
<td>2.68</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.64</td>
<td>1.21</td>
<td>1.19</td>
<td>1.04</td>
<td>2.18</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>56</td>
<td>67</td>
<td>75</td>
<td>70</td>
<td>81</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>4.79</td>
<td>5.61</td>
<td>2.56</td>
<td>3.72</td>
<td>4.22</td>
</tr>
<tr>
<td>Deco (ml/min/mm Hg)</td>
<td>13.6</td>
<td>18.1</td>
<td>13.5</td>
<td>15.3</td>
<td>21.3</td>
</tr>
</tbody>
</table>

*Predicted values are for 7/81, with negligible change over the 6 year period shown.

**Table 2—Pulmonary Function Tests of Case 2**

<table>
<thead>
<tr>
<th>Date</th>
<th>10/86</th>
<th>4/88</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (L)</td>
<td>1.86</td>
<td>1.78</td>
<td>2.77</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.08</td>
<td>1.68</td>
<td>2.23</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>58</td>
<td>61</td>
<td>80</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>2.76</td>
<td>3.76</td>
<td>4.48</td>
</tr>
<tr>
<td>Deco (ml/min/mm Hg)</td>
<td>15.8</td>
<td>15.8</td>
<td>21.8</td>
</tr>
</tbody>
</table>

**Figure 2.** Transbronchial biopsy of case 1. Focal emphysema and bronchitis are present, plus chronic interstitial inflammation and fibrosis consistent with a long history of bronchopulmonary infection.

The patient has continued to have frequent exacerbations of bronchitis and wheezing, which are moderately responsive to administration of bronchodilators, oral antibiotics, and short bursts of low-dose prednisone (maximum 15 mg/day).

**Case 2**

This patient is the non-identical twin sister of Case 1, raised in a different household several hundred miles away. Her clinical presentation was very similar to that of her sister, with paroxysmal cough, hemoptysis, and recurrent pulmonary infiltrates. She was also a non-smoker. On physical examination, crackles were heard over the posterior lung fields. No pathogens have been cultured from her sputum. Chest x-ray films showed evidence of fibrotic change. There was evidence of obstructive and restrictive disease on pulmonary function testing (Table 2).

Serum immunoglobulin class and subclass levels were normal except for IgE, which was <0.5 IU/ml. Specific antibody to tetanus and *H influenzae* type b were normal.

**Case 3**

The patient is the 38-year-old daughter of case 1. She suffered frequent episodes of pneumonia as a child, with limitation in exercise capability compared to her peers. She denied any smoking history. On physical examination, breath sounds were absent on the left side, and clubbing of the extremities was noted. A CAT scan revealed congenital absence of the left lung, with no evidence of vessels or bronchi on that side. There was evidence of obstructive lung disease on pulmonary function testing. Decreased lung volumes noted were likely due to the congenital lung agenesis, but restrictive disease of the other lung has not been ruled out. There was evidence of right ventricular hypertrophy on ECG. Serum concentrations of IgG, IgA, IgM, and IgG subclasses were normal, but IgE was <0.5 IU/ml.
Materials and Methods

Patients

Twenty-three family members of case 1, age range 2 to 64 years and spanning three generations, were questioned regarding their medical history, and records obtained whenever possible. Fourteen had a history of chronic or recurrent otitis media, sinusitis, pneumonia, or a combination of these. Twelve family members suffered frequent bronchopulmonary infections requiring multiple courses of antibiotics. Cases 1 and 2 had multiple radiographically documented episodes of pneumonia. Case 3 was the only family member with congenital agenesis of one lung. She also had at least one episode of pneumonia in the remaining lung, and suffers from chronic sinus infections. Several members of the family have been sufficiently compromised to necessitate hospitalization for pneumonia. Only one family member was a smoker.

Neurologic abnormalities suggestive of ataxia-telangiectasia, commonly associated with recurrent infection and IgE deficiency, were not present. However, one male member of the oldest generation studied has been institutionalized since infancy due to a congenital neurologic defect, and a nephew had idiopathic epilepsy since childhood.

Pulmonary Evaluation

Pulmonary function tests were done in six symptomatic and four asymptomatic family members. Except for case 2, all were performed at Harbor-UCLA Medical Center and interpreted by Dr. Richard Casaburi of the Department of Pulmonary Medicine. Other family members were not assessed due to inability of the younger children to cooperate, or inability to travel to our institution for this purpose.

Immunologic Evaluation

Blood samples from all 23 available family members were obtained. Sera were separated and immediately stored at −20°C until assays were performed for evaluation of humoral immunodeficiency.

Quantitation of IgG, IgM, and IgA: Serum concentrations of IgG, IgM, and IgA were measured by radial immunodiffusion (RID), using agarose gel plates containing class-specific antiserum (Kent Laboratories, Redmond, WA).

Quantitation of IgG subclasses: Serum concentrations of IgG subclasses 1-3 were measured by RID using commercially available kits from ICN Laboratories, Lisle, IL. Specificity was confirmed with purified myeloma proteins of each IgG subclass. Reference sera were standardized against WHO reference serum 67/97. IgG4 was measured by radioimmunoassay (RIA), as previously described.11

Quantitation of IgE: IgE determinations were also made by RIA.12 Affinity purified rabbit anti-IgE bound to CNBr-activated cellulose discs served as capture antibody. After incubation with test sera, 125I-labeled rabbit anti-IgE with specificity for a different E-chain epitope was used to detect bound IgE. IgE values were then read from a standard curve derived from serial dilutions of a previously standardized reference serum.

Measurement of specific IgG antibody to tetanus toxoid and PRP by RIA: Tetanus toxoid or PRP conjugated with poly-L-lysine (PRP-PLL) bound to cellulose discs served as antigen. 125I-labeled Staphylococcus protein A was used to detect bound IgG antibody. Reference sera with high known levels of specific antibody were used in each assay.

Results

Immunologic Evaluation

Of the 14 symptomatic family members suffering from recurrent or chronic sinopulmonary infections, 12 were found to have serum IgE levels less than 5 IU/ml (Fig 3). Of these, four had less than 1 IU/ml IgE. There was a striking difference between this

PEDIGREE OF FAMILY WITH IgE DEFICIENCY AND SINOPULMONARY DISEASE

![Pedigree of family with IgE deficiency and sinopulmonary disease](image)

**Figure 3.** Pedigree of family with IgE deficiency and sinopulmonary disease. Darkened circles and squares represent individuals with serum IgE <5 IU/ml. Slashes indicate family members who were not available for study. P = chronic or recurrent bronchopulmonary infections, S = chronic or recurrent sinusitis, and O = chronic or recurrent otitis media. Combinations of letters indicate concurrent symptoms involving more than one site.

Familial IgE Deficiency and Sinopulmonary Disease (Schoettler; Schleissner; Heiner)
group of family members and those who were asymptomatic, in that the healthy group all had IgE values well above 51U/ml, ranging from 10 to 92 IU/ml (Table 3). Fisher two-tailed exact test showed this difference between groups to be highly significant, with a p-value <0.0005.

Three adult family members had somewhat low serum IgA concentrations (70-90 mg/dl). Of these, two were also IgE deficient, both suffering recurrent infections. The only other associated immunoglobulin abnormality found was in the youngest family member tested, a two-year-old girl with recurrent otitis media, a history of pneumonia, and failure to thrive. IgG2 was extremely low (<10 mg/dl) in her serum, as was IgE (<0.5 IU/ml).

All persons tested had serum levels of IgG antibody to tetanus toxoid and PRF which are considered adequate for protection. The older members of the group tended to have less tetanus antibody than their younger relatives, probably due to the length of time since their last tetanus booster immunization.

Total IgG, IgA, and IgM were normal for age in all cases, as were IgG1, IgG2, and IgG4. The index case, case 1, had low normal levels of IgG, reflecting low normal amounts of IgG1, IgG2, and IgG4.

**Pulmonary Function Tests**

Pulmonary function studies were performed on ten family members. Six of the 14 family members symptomatic for recurrent or chronic sinopulmonary infection were tested. Of these, three had normal total lung capacity, vital capacity, and forced expiratory volumes (FEV1) for age and height. The remaining three had abnormal test results, as described above in their individual case reports (Tables 1 and 2). All four asymptomatic patients tested had normal lung volumes and flow rates.

**DISCUSSION**

The family described in the present study demonstrates an association between IgE deficiency and recurrent or chronic sinopulmonary infection. Progressive loss of pulmonary function occurred in the two oldest IgE-deficient family members who had evidence of pulmonary fibrosis. The presence of focal emphysema and fibrosis of the lung parenchyma on transbronchial biopsy may be a result of chronic pulmonary infection, although other etiologies of fibrosis remain possible.

Analysis of the three generations of the family presented in this article suggest autosomal dominant inheritance of IgE deficiency, with variable penetrance. Since IgE was decreased but not absent in most of these individuals, it is likely that a defect exists in the regulation of IgE production, rather than an aberration of the IgE heavy chain gene itself. The heavy chain genes for immunoglobulins are located on chromosome 14, with IgA1, IgG2, IgG3, IgE, and IgA2 in sequential order. Linkage of these may explain the tendency for deficiencies of these immunoglobulin classes and subclasses to occur simultaneously. Alternatively, a common regulatory mechanism may exist, with resultant suppression of heavy chain production for more than one immunoglobulin class or subclass. In the present study, decreased serum IgE was accompanied in three family members by subnormal levels of IgA, and in one child by a very low level of IgG2, suggesting a common down-regulatory mechanism.

Elevated serum IgE levels are often associated with pathologic states, as in atopic conditions, broncho-pulmonary aspergillosis, and Job's syndrome (hyper-IgE syndrome with recurrent infection). However, IgE may serve a beneficial role in some instances. This is true in certain parasitic infestations, such as Schistosoma mansoni, in which antiparasitic IgE antibody can be shown to aid in protection against the invading parasite by enhancing its destruction by macrophages. Specific IgE antibody directed against Staphylococcus aureus is found in persons with Job's syndrome, who have a predisposition for recurrent abscesses containing this organism, and serious bacterial infections of the respiratory tract. In this disease, higher total and S aureus-specific serum IgE levels are associated with less frequent infection at mucosal surfaces, compared with Job's syndrome patients with fewer of these antibodies. Thus, anti-bacterial IgE may afford some protection against infection in these patients.

IgE levels are often extremely low or undetectable in various immunodeficiency states, where low levels of IgE may accompany decreased levels of other immunoglobulin classes. Patients with multiple immunoglobulin class or subclass deficiencies tend to have frequent or severe infections, usually attributed to insufficient opsonins of the IgG or IgM class, but reports of isolated IgE deficiency in association with recurrent respiratory infections suggest involvement of this immunoglobulin in respiratory tract defense. In ataxia-telangiectasia, a neurologic syndrome in which recurrent bacterial infections are common, IgE deficiency has been found in up to 80 percent of

**Table 3—IgE Deficiency in Symptomatic vs Asymptomatic Family Members**

<table>
<thead>
<tr>
<th>IgE</th>
<th>Sinopulmonary Infection</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>(IU/ml)</td>
<td>(No. individuals)</td>
<td>(No. individuals)</td>
</tr>
<tr>
<td>&lt;1*</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>1-5*</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>&gt;5</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>9</td>
</tr>
</tbody>
</table>

*12 of 14 symptomatic, and none of the 9 symptomatic individuals studied, were IgE deficient (p <0.0005).
patients. Over half of these patients are deficient in both IgE and IgA; IgG4 and IgG1 deficiency is sometimes present as well.3,9,10 Ataxia may also present without telangiectasia, in association with IgE deficiency.81 However, IgE antibodies do not seem to be essential for health, since occasional healthy individuals may be found to have very low IgE levels.1,22

The precise role of IgE in immune defense is unclear. It may be involved in mucosal defense, along with secretory IgA. IgE-forming plasma cells are primarily located in mucosal tissues of the respiratory and gastrointestinal tracts, and in tonsillar and adenoidal tissue.23,24 IgE can be found in normal tracheobronchial secretions, and appears to be locally produced to a large degree.25 Perhaps IgE in mucosal secretions is important in normal resistance to invasion by respiratory pathogens. Lack of IgE could lead to impaired mucosal defense, with resultant susceptibility to respiratory tract infections.

Certain pathogenic organisms are capable of stimulating IgE production. The early immune response to Epstein-Barr virus (EBV) infection often includes a sharp rise in total serum IgE,26,27 followed by rises in serum concentrations of other immunoglobulin classes and subclasses. Production of IgE specific antibody to respiratory syncytial virus (RSV) has been demonstrated in RSV-infected children, associated with an increased prevalence of wheezing.28 Characteristics of both the host and the pathogenic organism are likely to be important in determining the degree and class of antibody response to a given infection, as well as the clinical effect of the response. There is no conclusive evidence that IgE antibodies per se are protective when detected in individuals infected with EBV or RSV. The effect of these antibodies on the course of disease may vary from one individual to another.

Direct IgE anti-viral or anti-bacterial activity may be important in the control of some infections, but in most instances, the amounts of serum IgE present are too minute to seem likely to act as neutralizing antibody when there is a large antigenic load, as in active infections. Alternative roles for IgE in immune defense might include action as a co-factor, with other immune factors needed for full protection. IgE in very small quantities has been shown to modify the microenvironment by its ability to trigger mast-cell mediator release, when two or more IgE molecules are bridged by an appropriate antigen, or by anti-IgE antibody.29,30 Chemical mediators from the mast cell can then alter vascular permeability, and in this way may allow access of various cellular and humoral immune components to the site of infection. Thus, IgE may indirectly aid in the clearance of invading pathogens, by initiating a cascade of events leading to mobilization of plasma components and cells from the intravascular pool. Steinberg et al31 have demonstrated in monkeys that the ability to neutralize intradermally injected diphtheria toxin was increased eight-fold when a non-related passive cutaneous anaphylaxis reaction was induced at the same location. Increased permeability caused by the IgE-mediated immediate hypersensitivity reaction may have promoted the passage of IgG antitoxin to the injection site of the toxin, supporting a "gatekeeper" role of local IgE in immune defense.

If IgE is indeed an integral part of the humoral defense system, by any of the above theorized actions, deficiency of this immunoglobulin would be expected to result in less efficient host resistance to infection. Alternatively, it is possible that IgE itself is not an important participant in host protection. Suppression of IgE production may accompany down-regulation of other immune factors. Perhaps the IgE deficiency noted in some individuals with recurrent sinopulmonary disease is a marker for a separate deficiency of an important molecule yet to be found.

In conclusion, this study demonstrates the familial occurrence of IgE deficiency with increased tendency to sinopulmonary infection in affected family members. Low serum IgE levels were in some cases accompanied by decreases of other immunoglobulins, indicating a possible abnormality of a putative gene regulator.

ACKNOWLEDGMENTS: We would like to thank Dr. Paul Dickman, Department of Pathology, Harbor-UCLA Medical Center, for his analysis of biopsy specimens. Dr. Richard Casaburi, Division of Pulmonary Medicine and Physiology, Harbor-UCLA Medical Center, for performance and evaluation of pulmonary function tests, and Mrs. Joy Heiner for expert secretarial assistance.

REFERENCES
4 Ammann AJ, Roth T, Hong R. Recurrent sinopulmonary infections, mental retardation and combined IgA and IgE deficiency. J Pediat 1970; 77:809-04
7 Stites DP, Ishizaka K, Fudenberg HH. Serum IgE levels in patients and family members and various immune deficiency states [abstract]. Clin Res 1971; 19:452
9 Ammann AJ, Cain WA, Ishizaka K, Hong R, Good RA. Immu-
13 Planagan JC, Rabbits TH. Arrangements of human Ig heavy chain constant region genes; implies evolutionary duplication of a segment containing gamma, epsilon, and alpha genes. Nature 1982; 300:709-13
15 Johansson SGO. Raised levels of a new immunoglobulin class (IgND) in asthma. Lancet 1967; 2:951-53
16 Patterson R, Roberts M. IgE and IgG antibodies against Aspergillus fumigatus in the sera of patients with bronchopulmonary aspergillosis. Int Arch Allergy Appl Immunol 1974; 46:150-60
19 Befus D, Bienenstock J. Factors involved in symbiosis and host resistance at the mucosa-parasite interface. Prog Allergy 1982; 31:176-77
20 Dreskin SC, Goldsmith PK, Gallin JI. Immunoglobulins in the hyperimmunoglobulin E and recurrent infection (Job's) syndrome. J Clin Invest 1985; 75:26-34