

IgA deficiency: clinical correlates and responses to pneumococcal vaccine

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Abstract

We surveyed historical and laboratory data for 127 IgA-deficient patients (ages 2–67), referred to an immunology clinic; the commonest medical history was recurrent respiratory infections (50%), followed by autoimmunity (28%) asthma and allergy (13%). Fifty-two subjects have been given a pneumococcal vaccination; vaccine responses to 12 serotypes were significantly related to serum IgG2 levels ($P = 0.004$). Six immunized IgA/IgG2-deficient subjects produced insignificant amounts of antibodies to these pneumococcal serotypes; 10 others with normal IgG2 levels also had subnormal vaccine responses. IgA-deficient patients who had at least one B8 allele ($n = 19$) had a significantly greater response to this vaccine than the HLA-B8-negative subjects ($n = 24$) ($P = 0.024$). There was no relationship between a history of recurring infections and pneumococcal vaccine responses; HLA status was not related to a history of autoimmunity.

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Introduction

Secretory IgA (sIgA) is synthesized by mucosal plasma cells and secreted into the gut, respiratory tract, and other exocrine secretions where it prevents absorption or attachment of bacterial and viruses to epithelial cells [1]. Selective IgA deficiency (IgAD) is the most common of the primary immunodeficiencies with a frequency between 1 in 400 and 1 in 2000 [2–7]. Although sIgA has a clear biological role [8], IgAD is a heterogeneous condition with symptoms ranging from none to recurrent respiratory or gastrointestinal diseases, atopy, asthma, inflammatory or autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, and pernicious anemia, [2,6,7]. B-cell maturation in IgAD is impaired [9], but the immunologic defect(s) remains unknown.

The inheritance of IgAD is usually sporadic but may occur in autosomal recessive or autosomal dominant forms [10,11]. Susceptibility to IgAD has been found linked to the HLA-DQ/DR locus and an extended major histocompati-

bility complex (MHC) haplotype [HLA-B8, SC01, DR3] has been found in increased frequency in both IgAD and common variable immunodeficiency [12–14]. IgAD is occasionally associated with IgG subclass deficiency [15], a combination that leads to severe bacterial infections [16,17]. For other IgAD subjects with normal levels of IgG2, but who have recurrent infections, no clear explanation has emerged. In these studies, we investigated the clinical conditions of a large group of subjects who were referred for IgAD. Fifty-two of these patients were immunized with a pneumococcal vaccine to evaluate antibody production to determine if these responses were related to gender, IgG2 level, HLA, or infection history.

Methods

Subjects and pneumococcal vaccination

The clinical and laboratory records of 127 IgA-deficient subjects (ages 2–67; median age 27) referred to the Division of Clinical Immunology at Mount Sinai Medical Center for consultation were reviewed. IgA deficiency was defined as an IgA less than 10 mg/dl while serum IgG and IgM were in the normal range for age. Fifty-two of these patients (median age 25), who could return for a second visit 4

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Age groups of IgA deficient patients

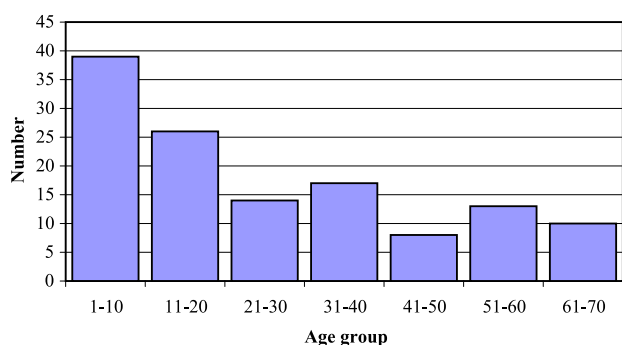


Fig. 1. Age at the time of referral for 127 IgA deficient subjects, given by decade.

weeks later, were immunized with a 23-valent pneumococcal vaccine (Pneumovax, Merck and Co., Inc., West Point, PA or Pnu-Imune, Lederle Pearl River, NY) and tested for vaccine responses. Medical histories were collected and reviewed on standardized forms.

Laboratory testing

Serum measurements (mg/dl) of IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgG, and IgM were determined and compared to age-related normals. HLA Class I and II antigens were determined by serological and/or molecular typing by standard methods [18]. Four weeks after pneumococcal vaccination, titers of IgG antibody to 12 serotypes (1, 3, 4, 6, 7, 8, 9, 12, 14, 18, 19, and 23) were determined by a radioimmunoassay with type specific antisera. No reagent showed inhibition with pneumococcal C-polysaccharide [19–22]. The nanograms of antibody nitrogen per milliliter (ng ab N/ml) were determined by reference to a standard curve and the geometric mean vaccine response was calculated [19–22]. A protective level of antibody to pneumococcal bacterial has not been established, although 200–300 ng ab N/ml has been considered a minimum protective level. However, normal control subjects produce a geometric mean response of more than 1000 ng ab N/ml [19–22]. In this study, we considered a geometric mean level of geometric mean level of 500–1000 ng/ml to be a blunted response, and responses between 0 and 500 ng/ml as an abnormally reduced response.

Statistical analyses

The Mann–Whitney test (Analyse-it Software Ltd. for Microsoft Excel) was used to compare differences in vaccine responses between patient groups, HLA status, and pneumococcal vaccine responses. The frequencies of recurrent infection among those who had a normal (above 1000 ng/ml), blunted (500–1000 ng/ml) or reduced pneumococcal geometric mean response (below 500 ng/ml), and

for relating HLA type and clinical illness, were compared using the Fisher's exact test. The Spearman's rank correlation coefficient test was used to examine the association between serum IgG2 and the pneumococcal geometric mean response.

Results

Serum immunoglobulin levels

For the 127 subjects, the median serum IgG for the 59 males was 1232 mg/dl, (range 480–3315 mg/dl); 68 females had a median IgG of 1345 mg/dl (range 542–3295 mg/dl). The IgM median for males was 108 (range 29–689 mg/dl); females had an IgM median of 160 mg/dl (range of 24–528 mg/dl) which was significantly more than males, $P = 0.014$. Based on age-matched normal levels, 10 of 127 IgA-deficient individuals (8%) had IgG2 deficiency; 37 had IgG3 deficiency (29%) and three (2%) patients had an IgG4 level less than 1 mg/dl.

Age at referral and clinical conditions

Patients were most commonly referred between the ages of 2 and 10; however, the mean age at the time of referral was 26 years (range 2–67) (Fig. 1). There were six main categories of reported illness among this group: recurrent infections, autoimmune disorders, allergy, cancer, and gastrointestinal disorders (Table 1). Patients with allergic symptoms or recurrent infections were younger (median ages 10.5 and 12.5) than subjects with a history of autoimmunity or gastrointestinal disease (ages 29 or 24.5); patients with cancer were older (median age 59) than other referred patients. Seven other subjects were healthy and IgAD was discovered either by chance or due to family history. The most common health condition cited in the collected historical information was recurrent infections (50%), with upper respiratory infections being the most frequent sub-category (Table 2). All 10 subjects with IgG2 subclass deficiency were in this group. Thirty-four subjects (28%) had one or more autoimmune diseases; females had significantly more autoimmunity than

Table 1
Clinical associations of referred IgA-deficient subjects^a

Condition	Number of patients	Patients (%)	Median age	IQR ^b years
Recurrent Infections	63	50	12.5	26.0
Autoimmunity	34	28	29.0	27.5
Allergy/Asthma	16	13	10.5	36.5
Cancer	9	7	59.0	15.0
Healthy	7	6	25.0	22.5
Gastrointestinal disorders	4	3	24.5	24.0

^a $N = 127$.

^b Twenty-nine patients (23%) had more than one of these conditions.

^c Interquartile range (age).

Table 2
Infections in IgA deficiency

Type	Number of patients
Recurrent Upper Respiratory Tract Infections	30
Pneumonia (one or more)	7
Acute or chronic otitis media	5
Chronic sinusitis	5
Chronic bronchitis	4
Urinary tract infection	2
Chronic obstructive lung disease with infections, chronic Lyme disease, lung abscess, alpha-1 anti trypsin deficiency with lung disease, bacterial sepsis, aseptic meningitis, recurrent tonsillitis, tuberculosis, chronic mastoiditis, acute rheumatic fever (one each)	10

N = 63.

males ($P = 0.01$) (Table 3). Idiopathic thrombocytopenic purpura was the most common autoimmune disorder. Ten other subjects had other conditions (chronic fatigue, anorexia, Factor X deficiency, exotoses, growth retardation, Guillain Barre, pulmonary fibrosis, severe graft-versus-host disease, post bone marrow transplant or chronic granulomatous disease, lymphadenopathy, mononucleosis, Sydenham's chorea or motor neuron disease).

HLA typing

Seventy-two of the 127 individuals had been HLA-A- and HLA-B-typed; 25 (35%) were heterozygous for HLA-A1 and 17 patients (24%) were heterozygous for HLA-A2. Of the typed patients, 27 (38%) had one B8 allele and one (1%) had two B8 alleles. The second most common HLA-B alleles were B7 (8%) and B44 (8%). Forty-three of the 127 had been typed for HLA-DR, and DR 1 was the most frequent (14%); 35 of the 127 had been HLA-DQ typed and DQ1 was the most common, 29%. The presence of HLA-B8 was not related to a history of autoimmunity.

Table 3
Autoimmunity in IgA deficiency

Type	Number of patients	
	Male	Female
Idiopathic Thrombocytopenic Purpura	2	5
Autoimmune Hemolytic Anemia	3	2
Juvenile Rheumatoid Arthritis	3	1
Autoimmune thyroiditis, Graves disease	0	3
Systemic Lupus erythematosus	1	2
Anti-nuclear antibody	1	2
Rheumatoid arthritis	1	2
Pernicious anemia	0	3
Diabetes mellitus	1	1
Morphea	0	1
Cryoglobulinemia	0	1
Autoimmune liver disease	0	1
Anti-sperm antibodies	1	0
Vasculitis	1	0
Total	14	24

N = 34.

Responses to pneumococcal immunization

Fifty-two subjects (age range 6 to 67, median age 25) had been given a pneumococcal vaccination and for whom vaccine responses could be determined after 4 weeks. Six patients with IgG2 deficiency were tested in this way; after vaccination, these patients had a median geometric mean response of only 83-ng ab N/ml (range 2–235). For the 46 patients with a normal serum IgG2 who were given this vaccine, the geometric mean post-vaccination response was highly correlated to the serum IgG2 level, $P = 0.004$ (Fig. 2). For these 46 subjects, the most immunogenic serotypes were 4, 8, 12, 18, and 23 (Table 4). Of these, the 31 females had a median geometric mean response of 1087 ng ab N/ml (range 39–4052), while the 15 immunized males had a median geometric mean response of 870 ng ab N/ml (range 288–2553, but not significantly different). Twenty of the 46 immunized subjects with normal IgG2 levels (43%), produced less than 1000 ng ab N/ml; 11 had geometric mean levels of 39–497 ng ab N/ml (abnormal) and 9 others had levels of 564–988 ng ab N/ml (blunted). The IgA-deficient subjects who had an HLA B8 allele ($n = 19$, 36% of the immunized group) had a significantly higher responses to pneumococcal vaccine than those who did not have this HLA type ($P = 0.024$). This enhanced response was predominantly due to an increased response to the pneumococcal serotypes 6, 9, 18, and 19 ($P < 0.05$). Of the immunized group of subjects, 35 patients (66%) had a history of recurring infections, including the 6 immunized IgG2-deficient patients. However, neither the presence of HLA-B8 nor the geometric mean antibody response to pneumococcal vaccine (for the 46 subjects who had a

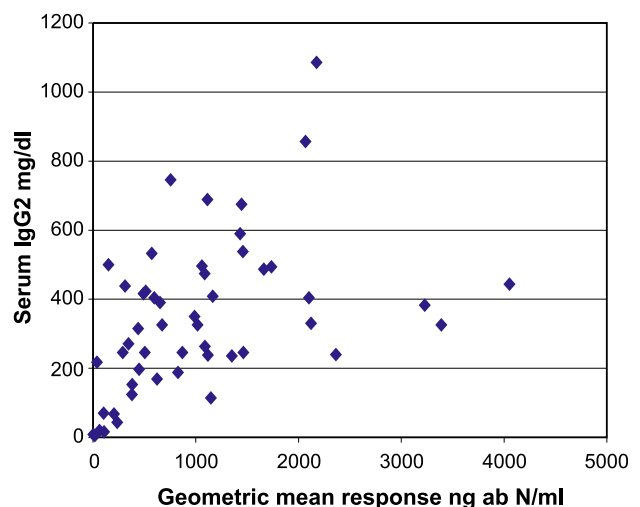


Fig. 2. The geometric mean response (in ng antibody nitrogen/ml of serum) for 12 pneumococcal serotypes, 4 to 6 weeks after vaccination by pneumococcal vaccine, as related to the serum IgG2 level (mg/dl) for 53 immunized subjects. There were six IgA IgG2 deficient subjects, all of whom had IgG2 levels under 100 mg/dl. Normal subjects, who are immunized with this vaccine, have a geometric mean of 1000 ng antibody nitrogen/ml or more in this assay.

Table 4
Levels of pneumococcal antibodies by serotype^a

Serotype	Median ^a	Minimum	Maximum
4	1839	34	12 372
8	1419	52	12 131
23	1251	1	15 721
18	1185	78	14 200
12	1185	1	5692
9	919	41	5680
7	915	59	8560
1	876	105	7000
3	834	1	7159
19	826	20	7200
14	625	0.5	11 828
6	605	31	11 300

N = 46.

^a For subjects with normal IgG2 levels (ng/antibody nitrogen/ml).

normal IgG2 level) was related to a history of recurrent infections.

Discussion

Some IgA-deficient individuals have no clinical symptoms and are healthy while others have recurrent illnesses. While patients with both IgA and IgG2 deficiencies are more prone to significant bacterial infections, other IgA-deficient subjects, some of whom have infections and others not, have not had distinguishing differences [2,6]. This lack of symptoms may be due to a compensatory increase in IgM-bearing B cells and increased secretory IgM in mucosal fluids [23,24]. However, one study did not find any association between salivary IgM levels and health or frequency of illness in 63 IgA-deficient subjects [25]. Since a deficiency mannan-binding lectin (MBL) can cause a defect in bacterial opsonization [26], the significance of MBL has also been explored in IgAD. However, MBL deficiency either alone or combined with IgG subclass deficiency was not significantly associated with increased susceptibility to infections [27].

Since in this group of IgA-deficient subjects, the most common reason for referral was recurrent infections, we explored antibody production to pneumococcal vaccine in 52 subjects, 35 of whom had this history. (Not significantly different from the group as a whole). For IgA-deficient subjects, the most immunogenic serotypes were 4, 8, 23, 18, and 12; for normal donors, serotypes 2, 3, 8, 9, and 14 have been reported to be the most immunogenic [28]. Twenty-six out of the 52 (50%) had reduced antibody production; as expected, this group contained six of the IgG2-deficient subjects who had been vaccinated [29,30]. (These subjects had a history of significant infections, and with demonstrated antibody deficiency are being treated with intravenous immune globulin). The 20 other subjects with normal IgG2 levels but abnormally low, or blunted antibody responses, are similar to previously reported IgAD patients who have subnormal antibody responses to carbohydrate antigens [29,31]. However, responses to pneumococcal vaccine are

known to be heterogeneous in normal healthy adults for genetic reasons, including inheritance of G2m(n) immunoglobulin allotypes [32–34]. However, the IgAD subjects in our group who had a blunted or even significantly reduced pneumococcal vaccine responses, were not likely to have had a history of recurrent infections than those subjects who had a normal vaccine response ($P = 0.1$).

Although a previous study found that the vaccine response to pneumococcal capsular polysaccharides was not related to HLA type in normal subjects [35], we found that IgA-deficient patients who had the B8 allele had a significantly higher geometric mean responses than those who did not. The reason for this is not known; the presence of histocompatibility antigens HLA-B8 and DR3 has been associated with a defect in expression of the reticuloendothelial system Fc-receptor, leading to the more prolonged circulation of IgG-containing immune complexes, as well as other immune differences [36,37]. In normal subjects who are homozygous for the MHC haplotype [HLA-B8, SC01, DR3,] subnormal responses to hepatitis B vaccine appear due to defects in Th1-type T cells [38–40]. While the HLA-B8, DR3 haplotype is also over-represented in certain autoimmune disorders (i.e., Graves' disease) [41], we also found no relationship between a history of autoimmunity and HLA-B8 in our patients.

In summary, while recurrent infections were the most common reasons for referral to this immunology clinic, pneumococcal vaccination responses for patients with this history were not worse than vaccination responses for those who did not. Thus, responses to this commonly used vaccine were not helpful in distinguishing between these two groups of patients. Curiously, IgA-deficient patients who had HLA B8 had significantly higher pneumococcal vaccination responses; on the other hand, this HLA type was not common in those patients with autoimmune disease.

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