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Multireactive Pattern of Serum Autoantibodies in Asymptomatic Individuals with Immunoglobulin A Deficiency

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Selective immunoglobulin A (IgA) deficiency (sIgAD) is associated with certain autoimmune states. Increased production of autoantibodies and eventual development of overt autoimmune disease are related in part to genetic and environmental factors as well as to the immune deficiency. We surveyed serum specimens from 60 healthy subjects with sIgAD for the presence of 21 different autoantibodies by enzyme-linked immunosorbent assays. The frequencies of 16 autoantibodies were higher in sIgAD patients than in normal healthy controls. Autoantibodies to Jo-1 (28%), cardiolipin (21%), phosphatidylserine (20%), Sm (15%), asialo-GM_1 (21%), sulfatide (32%), sulfoglucuronyl paragloboside (11%), and collagen type I (10%) were detected at high frequencies in comparison to those of normal healthy controls. Many of the serum samples were multireactive (i.e., exhibited binding to more than two autoantigens). Forty percent (24 of 60) of sIgAD serum samples reacted against six or more autoantigens; 10% (6 of 60) of sIgAD serum samples were not reactive with any of the 21 autoantigens. Three percent (7 of 209) of consecutive serum samples submitted for autoimmune antibody analysis that were positive for autoantibodies were from patients with IgA deficiency. Our finding of an increased frequency of autoantibodies in sIgAD patients supports the notion of polyclonal stimulation by repeated environmental stimuli as an etiologic mechanism. Alternatively, the increased frequency may be caused by a dysregulation of the immune response in such individuals. The mere detection of autoantibodies cannot predict whether a subject with sIgAD will develop an autoimmune disease or determine which specific disease will emerge.

Selective immunoglobulin A (IgA) deficiency (sIgAD), the single most common immunodeficiency state, occurring as frequently as 1 in 396 (30), is defined as serum IgA levels of <5 mg/dl (12, 35). sIgAD is generally considered a permanent genetically determined state with multifactorial etiologies (37). Despite the fact that the majority of sIgAD subjects are asymptomatic, this relatively benign immunodeficiency is associated with certain disease states and is found with increased frequency in patients with allergies, recurrent upper respiratory tract infections, gastrointestinal diseases, malignancies, and autoimmune diseases (4, 5, 13, 14, 17, 18, 21, 23, 33, 39, 57).

Included among the autoimmune disorders associated with sIgAD are systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, thyroiditis, celiac disease, Addison's disease, inflammatory bowel disease, Sjögren's syndrome, cerebral vasculitis, idiopathic thrombocytopenic purpura, pernicious anemia, lupoid hepatitis, and Coombs test-positive hemolytic anemia (4, 34). One extensive survey of sIgAD patients found that 37% have autoimmune disease or phenomena or both (5). Whether the abnormalities which lead to IgA deficiency in the absence of associated disease are the same as those that cause sIgAD with associated disease (e.g., autoimmune disease) is not known (28).

Previously, we reported the frequencies of 13 different autoantibodies in 49 patients with IgA deficiency (23). In this study, we have expanded our analysis to include 21 autoantibodies in sera from 60 additional subjects and compared the results with those of normal healthy controls.

MATERIALS AND METHODS

Sera. Sera from 60 healthy individuals (28 males, 32 females) with sIgAD (defined by serum IgA levels of <5 mg/dl) detected during screening of a healthy population and from 60 normal healthy controls were evaluated. Sera were stored at −70°C until tested. To determine the frequency of IgA deficiency in a cohort of patients with autoimmune conditions, 209 consecutive serum samples submitted for autoimmune antibody analysis that were positive for one or more autoantibodies (antinuclear autoantibodies, double-stranded DNA [dsDNA], Sm, ribonucleoprotein [RNP], Ro, La, Scl-70, and thyroid microsome antibodies) were analyzed.

Autoantigens. The following autoantigens were utilized to determine autoantibody concentrations by enzyme-linked immunosorbent assays (ELISAs): SS-A (Ro), SS-B (La), Sm, RNP, Scl-70, Jo-1, cardiolipin (ACA), phosphatidylserine, proteinase-3 (PR-3), myeloperoxidase, noncollagenous domain I of the glomerular basement membrane, collagen type I, thyroid microsome antibodies, acetylcholine receptor (AChR), histone (H2A-H2B)-DNA complexes, gangliosides GM_1 (monosialogangliosides) and asialo-GM_1, peripheral nerve sulfatide, sulfoglucuronyl paragloboside, dsDNA, and gliadin.

ELISAs. ELISAs were similarly performed for all antigens with slight modifications for some of the antigens as described. Microtiter plates (96-well plates) (Immulon I; Dynatech, Chantilly, Va.) were coated with the test antigens in bicarbonate buffer (pH 9.6), and glycolipids in 1:3 $CHCl_3$-methanol were coated by evaporation. Wells were blocked with 1% bovine serum albumin (BSA) in phosphate-buffered saline (PBS) and washed extensively with PBS. Sera were diluted 1:100 with PBS containing 0.05% Tween 20 and 1% BSA and applied to the wells. After repeated washings, gamma chain-specific goat anti-human IgG (diluted 1:2,000) conjugated to alkaline phosphatase (American Qualex, La Mirada, Calif.) was added. Bound antibody was determined by adding *p*-nitrophenyl phosphate substrate and reading the optical density at 405 nm on an automated plate reader. In all cases, the assays employed at least five standards, as well as positive and negative controls. Wells were blocked in 10% fetal bovine serum for cardiolipin; for autoantibodies to myeloperoxidase, PR-3, gliadin, *Brucella* and ribosomal P protein, goat anti-human IgG was employed at a 1:4,000 dilution. The detection of dsDNA antibodies was carried out by the Farr assay as previously described (36).

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TABLE 1. Frequencies of various autoantibodies in sera from asymptomatic individuals with sIgAD and normal healthy controls

Autoantigen[a]	Frequency (%) of autoantibodies[b]		P^c
	sIgAD	Normal	
dsDNA	16 (10/60)	0 (0/60)	0.003
SS-A (Ro)	8 (5/60)	1.5 (1/60)	0.21
SS-B (La)	1.5 (1/60)	0 (0/60)	1.00
Sm	15 (9/60)	1.5 (1/60)	0.021
RNP	7 (4/60)	0 (0/60)	0.127
Scl-70	5 (3/60)	0 (0/60)	0.242
Jo-1	28 (17/60)	0 (0/60)	0.00003
NC-I	3 (2/60)	0 (0/60)	0.476
Collagen type I	10 (6/60)	0 (0/60)	0.036
Cardiolipin	21 (13/60)	1.5 (1/60)	0.002
Phosphatidylserine	20 (12/60)	0 (0/60)	0.0008
PR-3	1.5 (1/60)	0 (0/60)	1.00
MPO	13 (8/60)	0 (0/60)	0.010
TMA	6 (4/60)	0 (0/60)	0.127
(H2A-H2B)-DNA complexes	1.5 (1/60)	0 (0/60)	1.00
GM_1	13 (8/60)	3 (2/60)	0.097
Asialo-GM_1	21 (13/60)	1.5 (1/60)	0.002
Sulfatide	32 (19/60)	0 (0/60)	0.000007
SGPG	11 (7/60)	1.5 (1/60)	0.067
AChR	0 (0/60)	0 (0/60)	
Gliadin	0 (0/60)	0 (0/60)	

[a] Abbreviations: NC-I, noncollagenous domain I; MPO, myeloperoxidase; TMA, thyroid microsome antibodies; SGPG, sulfoglucuronyl paragloboside.

[b] Numbers in parentheses are the number of individuals with autoantibodies to the total number of individuals tested.

[c] Chi-square analysis with Yate's correction.

For detection of autoantibodies to nerve antigens, 250 ng of the antigen in 1:3 $CHCl_3$-methanol was coated on the plates by overnight evaporation at room temperature; uncoated wells (background) were filled only with coating solution. The wells were blocked with 1% BSA in PBS for 30 min at room temperature and then washed with 0.05% Tween 20 in PBS. Portions (100 μl) of test sera and positive controls diluted 1:300 were incubated for 30 min at room temperature. Following repeated washings, bound antibodies were detected with a 1:2,000 dilution of goat anti-human IgM or anti-human IgG antibodies conjugated to alkaline phosphatase and developing with *p*-nitrophenyl phosphate substrate.

To detect AChR antibodies, AChRs were isolated from human skeletal muscle and radiolabeled by complexing with ^{125}I-labeled α-bungarotoxin. The labeled receptors were incubated with patient sera, and goat anti-human IgG was added in excess to precipitate the antibody-containing complexes. The precipitate was washed, the radioactivity in the pellet was determined, and the test sera were analyzed against a standard curve.

Statistical analysis. Results on the frequency of autoantibodies in the sIgAD individuals and normal controls were compared by chi-square analysis with Yate's correction.

RESULTS

The frequencies of 16 of the 21 autoantibodies tested were higher in sera from 60 asymptomatic sIgAD subjects than in normal healthy controls (Table 1). AChR, gliadin, SS-B, noncollagenous domain I, histone (H2A-H2B)-DNA complex, and PR-3 autoantibodies were detected at frequencies comparable to those in normal healthy controls. Autoantibodies to Jo-1 (28%), cardiolipin (21%), phosphatidylserine (20%), Sm (15%), asialo-GM_1 (21%), sulfatide (32%), and sulfoglucuronyl paragloboside (11%) and collagen type I (10%) were the most frequently detected. In many autoantibody-positive sera, the autoantibody concentrations exceeded that of the control serum with the highest positive results derived from patients with the respective clinically defined autoimmune disease.

Sixty-six percent (40 of 60) of the sIgAD serum samples were multireactive (i.e., binding to more than 2 autoantigens was readily detected); 40% (24 of 60) of these serum samples were reactive with 6 or more autoantigens, with reactivity profiles of up to 16 different autoantigens (Table 2). Ten percent (6 of 60) of the sIgAD serum samples had no autoreactivity against any of the 21 autoantigens. Other than the lack of autoreactivity, this group did not exhibit any specific abnormalities that would distinguish it from the multireactive group.

TABLE 2. Autoantibody multireactivity in sera from asymptomatic individuals with IgA deficiency

No. of autoantibodies detected	Frequency (%)[a]
0	10 (6/60)
1	12 (7/60)
2	12 (7/60)
3	8 (5/60)
4	10 (6/60)
5	8 (5/60)
6	15 (9/60)
7	8 (5/60)
8	8 (5/60)
9	3 (2/60)
10	2 (1/60)
11	2 (1/60)
16	2 (1/60)

[a] Numbers in parentheses are the number of individuals with autoantibodies to the total number of individuals tested.

In another study, 3% (7 of 209) of serum samples submitted for autoimmune testing which showed reactivity against one or more of the autoantigens (antinuclear antibodies, dsDNA, Sm, RNP, SS-A [Ro], SS-B [La], Scl-70, and thyroid microsome antibodies) used in a routine workup for autoimmunity, were IgA deficient. Elevated IgA concentrations were observed in 37% of these serum samples.

DISCUSSION

The well-documented and striking association of autoimmune diseases with sIgAD ranges from 7 to 36% in a large number of asymptomatic IgA-deficient patients (4, 34). Systemic lupus erythematosus (2.3%), rheumatoid arthritis (0.3%), juvenile rheumatoid arthritis (2.8%), Still's disease (3.4%), sarcoidosis, Sjögren's syndrome, scleroderma, and dermatomyositis are reportedly associated with IgA deficiency (34). Organ-specific diseases associated with IgA deficiency include insulin-dependent diabetes mellitus (0.02 to 2.2%), myasthenia gravis (0.7%), autoimmune thyroiditis, Addison's disease, pernicious anemia, vitiligo, primary biliary cirrhosis, chronic autoimmune hepatitis, autoimmune hemolytic anemia, and idiopathic thrombocytopenia purpura (34).

We sought to provide a comprehensive serosurvey of the frequencies of organ-specific and non-organ-specific autoantibodies in order to determine if distinctive patterns of autoantibody reactivities in sIgAD subjects can be discerned. There is ample precedent for an asymptomatic subject with an elevated concentration of a specific autoantibody (e.g., Sm or Jo-1) developing the respective specific autoimmune condition (7). Surprisingly, analysis of the frequencies of 21 different autoantibodies in 60 sIgAD individuals revealed polyreactive patterns of autoantibodies in most subjects. Sixty-six percent (40 of 60) had significantly increased concentrations of more than two autoantibodies; in 40% (24 of 60) of serum samples, there were 6 or more different specific autoantibodies. In one serum sample, a phenomenal plethora of autoantibodies reacted with 16 different autoantigens! How can such findings be explained? Clearly, a common epitope is unlikely among such diverse

molecules, since this kind of reactivity is not observed in any selective disease population. A polyclonal reaction with many individual autoantibodies present in the serum of the same individual is equally unlikely.

Individuals with IgA deficiency are known to suffer from recurrent respiratory and gastrointestinal infections (11, 18, 41). A variety of viruses, bacteria, and parasites could induce the production of many individual non-cross-reactive autoantibodies by mechanisms such as polyclonal activation (22) or molecular mimicry (25), as well as the production of a population of cross-reactive autoantibodies. A similar phenomenon was recently noted in Guillain-Barré syndrome, which is known to be preceded by infections with diverse viruses and bacteria (45). Indeed, sera of patients with Guillain-Barré syndrome contain a variety of autoantibodies reactive with a variety of antigens including glycolipids (45) and glycoproteins (46), i.e., mostly autoantigens without discernible cross-reactive epitopes.

As yet, it is unclear if the pattern of autoantibody reactivity in sIgAD patients will be useful for predicting development of overt autoimmune disease in asymptomatic subjects. The unresolved issue of the predictive value of detection of autoantibodies for development of the related disease in sIgAD is of special importance when the autoantibodies detected are associated with the development of a specific disease, as is the case for pyruvate dehydrogenase antibodies and primary biliary cirrhosis, for which treatment with ursodeoxycholic acid is effective (42, 60).

A very important question remains to be answered: why does one patient with IgA deficiency develop autoimmune hemolytic anemia, whereas another develops rheumatoid arthritis? We believe that IgA deficiency is one of multiple risk factors for autoimmunity including complement component deficiencies (e.g., C2 and C4), suppressor T-cell defects, and female gender (9, 50, 52, 53). Whether an autoimmune disease will emerge in an individual with IgA deficiency is determined by a combination of genetic and environmental factors found in the specific subject, a phenomenon referred to as "the mosaic of autoimmunity" (53).

The prevalence and variety of autoantibodies in subjects with IgA deficiency are skewed toward rare, highly disease-specific autoantibodies such as Jo-1 (28%), Sm (15%), and antiphospholipid antibodies (20%). Such patterns in sIgAD could reflect invasion of the deficient mucosa by specific infecting agents because similar patterns of autoantibodies have not been reported in the absence of sIgAD. Indeed, although systemic lupus erythematosus is reported in IgA-deficient individuals (2.3%) (2, 13, 20, 23, 59), dermatomyositis and the antiphospholipid syndrome are not reported in IgA-deficient individuals. Of similar interest is the fact that although myasthenia gravis can occur in conjunction with IgA deficiency (0.7%) (8, 10, 33), we found no increased frequency of AChR antibodies among our cohort of sIgAD subjects. As in the current study, increased frequencies (37 to 53%) of antiphospholipid antibodies were reported in previous studies of sIgAD patients (20, 23, 29). Common infections can induce antiphospholipid antibodies, albeit with different characteristics than phospholipid antibodies not associated with infection (44). A similar relationship to infection could explain the relatively increased frequency of myeloperoxidase antibodies (24%) in comparison to the lack of PR-3 antibodies among subjects with IgA deficiency (48).

The high frequencies of autoantibodies in sera of subjects with IgA deficiency have been attributed to the following: suppressed T-cell activity (35, 54); increased absorption of food and other exogenous antigens, leading to chronic antigenemia and the resultant production of cross-reactive antibodies (21, 51); genetic factors, such as the HLA-A1, -B8, and -DR-3 phenotype (3, 49) commonly observed both in patients with autoimmune disorders and in healthy autoantibody-positive relatives of patients with autoimmune diseases (55); and immunoregulatory defects in healthy individuals (54).

The extent of polyclonal activation in the sIgAD sera evaluated in this study could result from expansion of natural autoantibodies. Such autoantibodies, usually IgM, are polyspecific with low affinities for their autoantigens (1). Yet, as in our study, IgG autoantibodies are well recognized (7). The fact that most subjects with IgA deficiency harboring autoantibodies are asymptomatic supports this notion.

Chronic, polyclonal stimulation of the immune system in IgA-deficient subjects could reflect lack of antigenic exclusion of food macromolecules and microbial compounds. Indeed, IgA-deficient subjects have increased intestinal permeability to macromolecules (40), and some have large amounts of dietary proteins in their serum (16). Moreover, precipitating antibodies against cow's milk antigens (casein, α-lactalbumin, β-lactoglobulin, and BSA) are found in 36 to 75% of IgA-deficient individuals, but in only 0.3% of controls (15, 21, 31). Antibodies to other dietary antigens such as fish, egg yolks, chicken, and pork serum are also detectable in IgA-deficient subjects (6). Similarly, concentrations of antibodies to respiratory viruses are higher in blood donors with sIgAD than in those with normal IgA concentrations (43). All of these data suggest an increased penetration by foreign antigens but can also reflect excessive and perhaps defective (e.g., lack of affinity maturation) immune responses in IgA-deficient subjects.

It should be emphasized that IgA deficiency has an additional common denominator with autoimmune disease: both autoimmune diseases and IgA deficiency are more prevalent among subjects with HLA-A1, -B8, and -DR3 (19, 24, 26, 32, 37, 58). Similarly, a higher frequency of C4A null alleles as well as C4A and 21-hydroxylase gene deletions are common in both conditions (38, 47). Last, but not least, it was recently shown that sIgAD is associated with non-Asp residues at position 57 of the HLA-DQ β chain (38), which has also been reported for insulin-dependent diabetes mellitus (56).

In most previous studies, sera of patients with IgA deficiency were analyzed for the presence of a few autoantibodies. In the current survey, we tested for the presence of 21 disease-related autoantibodies, many of which were detected in sIgAD for the first time. The challenge is to determine which patients with sIgAD will develop autoimmune diseases. In addition to the genetic predisposition (e.g., HLA-A1, -B8, and -DR3 and C4A null alleles) and the capacity to synthesize autoantibodies, there are still one or more pieces missing from the mosaic. Perhaps affinity maturation of the autoantibodies will prove to be an important predictor for development of the relevant autoantibody- or cell-mediated disease.

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