Progression of Selective IgA Deficiency to Common Variable Immunodeficiency

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Key Words

Common variable immunodeficiency · IgA deficiency · Antibody deficiency

Abstract

Selective IgA deficiency (IgAD) is the most common primary immunodeficiency in Caucasians. Although it is often asymptomatic, selected patients show an increased frequency of infections, allergies and autoimmune manifestations. Common variable immunodeficiency (CVID) is a primary antibody deficiency disease that shares many clinical features with IgAD. A common genetic basis for IgAD and CVID has been suggested based on their occurrence in members of the same family and the similarity of the underlying B cell defects. Progression from IgAD to CVID has also been reported in several cases. Here we present 4 patients with IgAD and autoimmune features who subsequently developed CVID. All symptomatic IgAD patients, especially those with associated IgG subclass deficiency or autoimmune features, should be monitored for evolution to CVID. Early diagnosis of this conversion and institution of immunoglobulin therapy is effective in preventing severe bacterial infections and pulmonary insufficiency.

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Introduction

Selective IgA deficiency (IgAD) is the most common primary immunodeficiency disorder and is characterized by decreased serum IgA concentration of <0.07 g/l and normal serum IgM and IgG levels [1]. Many of these individuals have no apparent disease, whereas selected patients suffer from recurrent mucosal infections, allergies and autoimmune diseases [2]. The defect is presumed to result from impaired switching to IgA or a maturational failure of IgA-producing lymphocytes.

Common variable immunodeficiency (CVID) is a primary antibody deficiency disease characterized by low serum levels of IgG, IgA and/or IgM, and normal or decreased B cell numbers leading to recurrent infections noted mostly in the respiratory and gastrointestinal tract [1, 3–5]. The pathogenesis of CVID still remains unknown. It seems that a defect in B cell differentiation leads to impaired secretion of immunoglobulins in the patients. Abnormalities of T cells and dendritic cells have also been reported in some patients [6–9].

A common genetic basis for IgAD and CVID has been suggested by their occurrence in members of the same family and the similarity of the underlying B cell defect [10]. Progression from IgAD to CVID has also been reported in several cases [11–13].

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Table 1. Laboratory findings of IgAD patients who progressed to CVID

Patient No.	Country	HLA	Date	IgM	IgG	IgA	IgG1	IgG2	IgG3	IgG4
1	Sweden	A1,1	01/12/1982	0.34	5.0	<0.05	2.92	0.03	0.39	<0.0
		B8,8	11/12/2003	<0.04	1.65	<0.02	–	–	–	–
		DR3,3	03/02/2004	0.04	1.57	<0.06	1.17	<0.08	0.23	<0.03
		DQ2,2	06/23/2004	<0.17	7.26 ¹	<0.06	4.17	3.06	0.30	<0.03
			03/03/2005	<0.04	8.04 ¹	<0.06	–	–	–	–
2	Sweden		01/16/1992	0.56	4.9	0.01	–	–	–	–
		B8,47	05/11/1992	0.3	6.0	<0.07	3.5	2.0	0.3	<0.05
		DR3,4	08/27/1998	0.4	4.3	0.08	2.5	1.8	0.6	0.27
		DQ2,3	11/20/2001	0.09	11.3 ¹	<0.06	5.37	5.11	0.35	0.06
			04/07/2004	0.07	10.1 ¹	<0.06	6.25	4.96	0.36	0.04
3	Iran	A2,29	08/15/1998	1.12	14.7	0	–	–	–	–
		B7,51	04/20/2000	0.8	8.6	0	6.72	0.51	0.6	0.03
		DR3,11	07/29/2002	0.2	3.4	0	–	–	–	–
		DQ2,3	02/26/2004	0.4	4.89	0	2.87	0.79	0.23	0.2
4	Spain	A1,2	1994	0.85	9.84	0	6.00	2.20	0.43	0.04
		B58,58	2001	0.25	4.40	0	3.60	0.02	0.30	0.1
		DR7,13	2005 ¹	0.15	7.53	0	5.12	2.63	0.42	0.3

Data are presented as grams per liter. ¹ Gamma globulin substituted.

In addition, fixed haplotypes of MHC genes are frequently associated with both IgAD and CVID. At least 2 distinct loci, 1 in the class II region and 1 in the class III region, confer susceptibility to the development of IgAD and CVID [3, 14]. The extended haplotype HLA-A1, B8, DR3 has been shown to be associated with both IgAD and CVID [10].

Two studies have recently reported that coding variants in *TNFRSF13B*, which encodes transmembrane activator and CAML interactor (TACI), are associated with CVID and IgAD [15, 16].

IgA deficiency is associated with some autoimmune diseases such as systemic lupus erythematosus, juvenile-onset diabetes mellitus and rheumatoid arthritis [17–19]. Homozygosity for the HLA B8, DR3, DQ2 haplotype or part of this haplotype is a risk factor for development of some autoimmune diseases [20–26].

Early diagnosis of conversion from IgAD to CVID and institution of immunoglobulin therapy is effective in preventing severe bacterial infections and pulmonary insufficiency [27]. Here we present 4 patients with IgAD that progressed to CVID, and review the reported cases in the medical literature to search for the effect of some factors such as HLA and autoimmune association [11–13, 28–36].

Materials and Methods

Study Population

The study was approved by the Tehran University of Medical Sciences and the Karolinska Institute in Stockholm. The clinical records of all immunodeficient patients were reviewed in these clinics for the past 20 years. Four patients are described here (2 Swedish, 1 Iranian and 1 Spanish).

Serum Immunoglobulin Levels

Serum immunoglobulin levels were determined by ELISA and nephelometry using goat polyclonal antisera. A sample was considered IgAD if the concentration of IgA was <0.07 g/l. The diagnosis of CVID was made when serum levels of at least 2 serum immunoglobulin isotypes (IgG, IgM and IgA) were lower than normal [37, 38].

HLA Typing

Samples were genotyped at the HLA A, B, DR and DQ loci by PCR-SSP [39]. Analysis of the *TNFRSF13B* gene (sequencing or analysis of disease-associated SNPs) was performed as described previously [16].

Case Reports

Patient 1

A 62-year-old man was identified as IgAD in 1974 during a routine screening of Swedish blood donors. Initially, he did not

Table 2. Characteristics of reported IgAD patients who progressed to CVID

Case	Sex	Interval of progression years	Characteristics of individual patients				Ref.
			clinical finding	immunological abnormalities	genetic association	family history	
P1	F	27	sinusitis, dermatitis, oral candidiasis, ITP, vitiligo	HIV infection, CD4 lymphopenia	18q deletion	–	12
P2	F	6	weight loss, chronic active hepatitis, vitiligo	NA	HLA A11,24, B38,39, DR3,4	–	11
P3	F	1	respiratory infection, systemic lupus erythematosus	ANA, anti-dsDNA, Antihiston, antimicrosomal	HLA A3,26, B18,51, DR1,4	–	11
P4	F	12	respiratory and gastrointestinal infections	IgG2 deficiency	NA	–	11
P5	M	5	recurrent pneumonia and tonsillitis	IgG2 and IgG4 deficiency	NA	NA	13
P6	M	4	recurrent infections	CD4 lymphopenia	NA	NA	13
P7	F	9	pneumonia, diabetes mellitus, thyroiditis	IgG2 and IgG3 deficiency	18q deletion	NA	32
P8	F	5	recurrent infections, ITP, autoimmune hemolytic anemia, Sjogren's syndrome	CD4 deficiency	NA	NA	29
P9	M	1.5	recurrent pneumonia	CD4/CD8 decreased	NA	+	30
P10	F	4	respiratory infections, diarrhea, alopecia	NA	NA	NA	31
P11	F	–	recurrent infections, chronic ITP	IgG2 and IgG4 deficiency	NA	+	33
P12	M	8	recurrent sinusitis	IgG2 and IgG4 deficiency	HLA A1, B8, DR3,4	+	34
P13	M	2	recurrent sinusitis, otitis media	IgG2 and IgG4 deficiency	HLA A1,31, B7,8, DR2,3	NA	34
P14	F	15	sinusitis, otitis media, bronchitis	NA	HLA A1,2, B44,49, DR7,13	–	34
P15	M	7 months	ulcerative colitis, amyloid changes, non-A/non-B hepatitis, bronchopneumonia, lichen planus	low B cells; defect in B and T cells	ND	–	35
P16	M	11	sarcoidosis, respiratory tract infection, bronchopneumonia	low B cells	HLA B7,40, DR4,4, DQ3,3	NA	35
P17	M	4	respiratory tract infection, measles, pneumonia, diarrhea	B cell defect; decreased number of CD20 cells; IgG1, 2, 3, 4 deficiency		NA	34
P18	M	7	ITP	IgG subclass deficiency and low isoheamagglutinins; nonreactive DHST, transient antithyroid and antiplatelet Ab	–	NA	28
P19	F	15	respiratory tract infection, nephrotic syndrome	IgG subclass deficiency and low isoheamagglutinins; nonreactive DHST, transient antithyroid and antiplatelet Ab	–	NA	28
P20	F	7	pneumonia, JRA, thyroiditis	IgG subclass deficiency and low isoheamagglutinins; nonreactive DHST, transient antithyroid and antiplatelet Ab	–	NA	28

ITP = Idiopathic thrombocytopenic purpura; ANA = antinuclear antibody; DHST = delayed hypersensitivity skin test; ND = not determined; Ab = antibody; JRA = juvenile rheumatoid arthritis; NA = not available.

experience increased infection susceptibility. However, a few years ago, he noted an increased proneness and a longer duration of infections, especially in the upper respiratory tract. *Haemophilus influenzae* was a common inciting organism. He was then diagnosed as CVID. Nevertheless, he had antibody against tetanus and diphtheria due to vaccination (table 1). He was adopted, thus no family history could be obtained. No mutations in the

disease-associated *TNFRSF13B* SNPs (C104R, A181E, R202H) could be identified.

Patient 2

A 53-year-old man was prone to otitis media during childhood but had no major infections until 1991. He had a previous history of mild psoriasis and influenza in 1991, when IgA deficiency was

detected by chance. He was referred to our clinic in Sweden in 1992 for evaluation. The patient is diabetic, as is his aunt and maternal grandmother. He was initially followed up without any treatment. Then, immunoglobulins started to drop, suggesting CVID (table 1) and gamma globulin treatment was started in 2001. Mutation analysis revealed no disease-associated mutations in *TNFRSF13B*.

Patient 3

A 21-year-old woman, the second child of consanguineous parents without a family history of immunodeficiency, had a history of recurrent infections from early childhood. Her medical problems began during infancy with allergic dermatitis, followed after 1 year by chronic diarrhea and frequent episodes of upper respiratory infections, including sinusitis and otitis media. At the age of 3, she was diagnosed with myasthenia gravis. At the age of 12, she was diagnosed with hypothyroidism and since that time, she has been treated with levothyroxin. At the age of 15, she developed a severe pneumonia and was hospitalized in the Children's Medical Center in Tehran for further evaluation, which showed undetectable IgA and diminished IgG2 in serum. Within 2 years of follow-up, serum levels of IgG and IgM showed a gradual decline and she subsequently developed bronchiectasis. From this point onwards she was considered to have CVID and has been substituted with intravenous immunoglobulin (table 1). Because of chronic diarrhea and growth retardation, a gastrointestinal biopsy was performed, which showed intestinal inflammation and subtotal villous atrophy.

Patient 4

A 20-year-old woman was admitted to hospital because of repeated episodes of diarrhea and respiratory infections, which improved with antibiotics. There was a history of juvenile rheumatoid arthritis in her brother. At the age of 14, she suffered from pneumonia, and IgAD with lymphoid nodular hyperplasia in the small intestine was diagnosed. No specific therapy except antibiotics and diet was given. She was referred again at the age of 26, due to persistent respiratory and gastrointestinal infections (*Giardia lamblia* and *Salmonella enteritidis*) with a decline in IgG, IgM and IgG2 levels, and a very poor response to pneumococcal vaccination. Consequently, CVID was diagnosed (table 1). She has been on intravenous immunoglobulin therapy since then and her clinical manifestations have improved greatly. Mutation analysis revealed no disease-associated mutation in *TNFRSF13B*.

Discussion

The characteristics and intervals until development of CVID in IgAD patients in previously published studies are summarized in table 2. The true number of cases is, however, probably much higher than that reported in the literature.

Progression of IgAD to CVID occurs in some families, but is not a general rule. On the other hand, it is postulated that only a subset of CVID is genetically related to IgAD; these are likely CVID cases with IgAD/CVID rel-

atives [10, 40, 41]. Although we did not study antibody responses against polysaccharide vaccines in all patients, it seems that some CVID patients can produce protective postvaccination titers [42], in contrast to the general notion that patients with CVID respond poorly to vaccination [38]. IgAD is occasionally associated with IgG subclass deficiency that may lead to bacterial infections and could signal the onset of CVID [43–46]. All but 2 of the reviewed cases had respiratory infectious manifestations, 47% had IgG2 subclass deficiency, indicating a gradual onset of CVID (table 2). Mutations of the gene *TNFRSF13B* encoding TACI have been found in some patients with CVID and IgAD [15, 16, 47]. However, the role of *TNFRSF13B* mutations in isolated IgAD has recently been challenged [48, 49]. No disease-associated mutations in *TNFRSF13B* were found in the 3 patients analyzed in this paper.

Co-occurrence of psoriasis and myasthenia gravis in our patients (table 1) and the frequency of 42% of IgAD patients with autoimmune disorders (table 2) suggest that autoimmunity could be a risk factor for progression to CVID.

Some extended MHC haplotypes such as HLA B8, DR3, that are unique in their association with a large number of autoimmune disorders, have also been found in increased frequency in both IgAD and CVID [10, 20, 50–53]. Our patients and others who have progressed from IgAD to CVID and have been HLA typed, share some alleles of these extended haplotypes (table 1). Several other extended haplotypes are increased in frequency among IgAD and CVID patients, including HLA A28, B14 and HLA A1, B8 [14, 44, 45, 54].

Homozygosity for HLA A1, B8, DR3, DQ2, or part of this haplotype, is a risk factor for development of IgAD, CVID and some autoimmune diseases such as celiac disease, myasthenia gravis, Graves' disease and systemic lupus erythematosus [10–12, 32, 50, 55]. Patient 1 is homozygous for HLA B8, DR3, DQ2 and patient 2 is heterozygous for this haplotype. Patient 3 is heterozygous for DR3, DQ2 (table 1). Thus, HLA A1, B8, DR3 and DQ2 homozygosity or heterozygosity in IgAD patients could be one of the factors that may be important for the progression to CVID.

Conclusion

Co-occurrence of some autoimmune disorders, IgG subclass deficiency and association of the HLA A1, B8, DR3, DQ2 or part of this haplotype in IgAD patients, in

particular those with affected family members, could be risk factors for induction of CVID, and monitoring these patients as well as substitution with gamma globulin could be effective for limitation of the signs and symp-

toms. It could be recommended that all symptomatic patients with IgAD should be carefully monitored for possible progression to CVID. Family studies in such a group of patients are also suggested.

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