Rheumatologic Manifestations in Patients With Selected Primary Immunodeficiencies Evaluated at the University Hospital

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Objective. **To characterize an IgA deficient and common variable immunodeficiency (CVI) group of patients in terms of the presence of rheumatologic manifestations.**

Background. **Although the molecular basis of some of the primary immunodeficiencies has been elucidated, it has not been possible to explain why in most cases these conditions are often associated with autoimmune manifestations, besides infections. The concomitant inability to fight infections adequately (immunodeficiency) and an inordinate reaction of the immune system to self components (autoimmunity) has been a perplexing situation.**

Methods. **The clinical and immunological profile of 71 patients fulfilling the diagnostic criteria of selective IgA deficiency (n=38) and common variable immunodeficiency (n=33) were evaluated for concurrent rheumatologic manifestations after a thorough medical history, physical examination and pertinent immunological parameters.**

Results. **The most common autoimmune conditions identified in patients with selective IgA deficiency were Crohn's disease and systemic lupus erythematosus (SLE); while immune thrombocytopenic purpura and Crohn's disease were the most common disorders associated to CVI. Anti-IgA antibodies were only found in 26.6% (95% C.I. 10.1-51.4) of patients with selective IgA deficiency but were present in all patients with that condition and SLE. Fifty per cent patients with CVI and ITP exhibited ANA positivity.**

Conclusions. **The IgA-deficient group of patients in this study showed a higher prevalence of autoimmune conditions and greater positivity for ANA as compared to patients with CVI. In contrast to other reports with around 44% positivity of anti-IgA antibodies in selective IgA patients these were only present in 26.3% of patients with that disorder in this study. The high prevalence of antinuclear antibodies not associated with any clinical autoimmune condition in the IgA-deficient patients in this study will need to be further explored to ascertain why IgA-deficient patients may be at an increased risk of autoimmunity. Inflammatory bowel disease (Crohn's disease and ulcerative colitis) constituted the most common clinical autoimmune manifestations in both groups of patients studied. ITP was the commonest organ-specific autoimmune condition identified in the CVI group, as reported in previous publications. The limited number of patients studied does not allow a reliable estimate of the prevalence of SLE in the IgA-deficient population analyzed. The observed differences in frequency of positive antibodies and clinical autoimmune conditions in our patients cannot be taken as typical due to the limited number examined and the exclusion of pediatric cases in the IgA deficient group. A continued surveillance of these patients might help to establish more definite tendencies regarding rheumatoiogic manifestations in primary immunodeficiencies.**

Key words: Primary immunodeficiencies, selective IgA deficiency, common variable immunodeficiency (CVI), autoimmunity

Primary immunodeficiencies comprise a diverse group of conditions which are traditionally classified according to the component of the immune system that is predominantly affected. Over one hundred such conditions have been characterized so far. B-cell antibody defects account for around 50% of them, selective IgA deficiency being the most common, followed by common variable immunodeficiency (CVI). Although, the molecular basis of a number of these conditions has been elucidated it has not been possible to explain why in most cases these immunodeficiencies are often associated with autoimmune manifestations, besides infections. The coexistence of an inability to fight infections adequately (immunodeficiency) and an inordinate reaction of the immune system to self components (autoimmunity) is a contradictory and vexing situation.

IgA deficiency and CVI share common clinical

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presentations especially those related to the gastrointestinal tract, i.e. inflammatory bowel disease, malabsorption syndromes and allergic manifestations. Both conditions also share autoimmune/inflammatory manifestations which may be limited to a single target organ, i.e. autoimmune hemolytic anemia (AHA), immune thrombocytopenic pupura (ITP), autoimmune thyroiditis or involve a number of different organs, i.e. systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), progressive systemic sclerosis (1,2).

The aim of this study was the characterization of a population of patients with IgA deficiency and CVI in terms of the presence of rheumatologic manifestations.

Methods

Study patients. The study group comprised patients followed at the Immunology Clinic of the University Hospital with diagnoses of selective IgA deficiency and CVI. A total of 38 patients with IgA deficiency and 33 patients with CVI were included in the study. Every patient underwent a complete history, physical examination and baseline laboratory tests through a uniform protocol used in the clinic. For inclusion in the study, IgA deficient patients had to be 20 years or older, so as to exclude patients with borderline levels related to young ages. All patients entered in the study had to be able to complete evaluation forms, have the capacity to give informed consent and agree to comply with sample drawing and serial visits. The population studied was followed for a period of ten years.

Immunological parameters. All patients were confirmed to have IgA deficiency or CVI on the basis of clinical presentation and immunoglobulin levels assayed in two fresh serum samples analyzed in separate reference laboratories. The methodology used for antibody assays was nephelometry. IgA deficiency was defined as an IgA level less than or equal to 10 mg/dl. CVI was identified as IgG, IgA and Ig M levels below normal range, as defined by age-dependent values. In addition, patients with panhypogammaglobulinemia had B cell counts performed using flow cytometry to exclude other primary immune defects. Antibody assays performed were: antinuclear antibodies (ANA) by indirect immunofluorescence, rheumatoid factor (by enzyme immunoassay) and anti-IgA by enzyme-linked immunosorbent assay. Any rheumatologic and/or autoimmune condition present in the patient population was diagnosed by standard criteria and American Rheumatism Association criteria.

Statistical analysis. Frequency distributions, percentages and their 95% confidence intervals were computed for categorical variables.

Results

The profile of IgA deficient patients included 20 men and 18 women between the ages of 20 to 63 years; the CVI population consisted of 23 women and 10 men from 5 to 42 years of age. As previously reported, the most common clinical presentation in both groups was infection (3, 4). Table 1 describes the rheumatologic conditions identified in IgA-deficient patients. Crohn's disease and systemic lupus erythematosus (SLE) constituted the majority of those conditions. The rheumatologic manifestations observed in the CVI patients are presented in table 2.

Table I. Rheumatologic manifestations in patients with selective IgA deficiency (n = 38)

Condition(s)	# patients	%	95% CI
IgA deficiency+Crohn's	6	15.8	6.6–31.9
IgA deficiency+SLE	5	13.2	4.9–28.9
IgA deficiency+ulcerative colitis	3	7.9	2.1–22.5
IgA deficiency+rheumatoid arthritis	2	5.3	1.0–19.1
IgA deficiency+scleroderma	1	2.6	0.1–15.4
IgA deficiency alone	19	50.0	33.7–66.3

Table 2. Rheumatologic manifestations in patients with common variable immunodeficiency (n = 33)

Condition(s)	# patients	%	95% CI
Systemic autoimmune disease			
CVI + SLE	2	6.1	1.1–21.6
CVI + R.A.	1	3.0	0.2–17.5
Organ-specific disease			
CVI + ITP	4	12.1	4.0–29.1
CVI + Crohn's	3	9.1	2.4–25.5
CVI + hypothyroidism	1	3.0	0.2–17.5
CVI + AHA	1	3.0	0.2–17.5
Other			
CVI + septic arthritis	2	6.1	1.1–21.6
CVI + aseptic arthritis	6	18.2	7.6-36.1

Immune thrombocytopenic purpura (ITP) and Crohn's disease were more frequently noted in this group. The only two patients with SLE in the group had CVI diagnosed after the initial autoimmune condition and off immunosuppressive therapy. Aseptic arthritis was mostly related to the CVI patient group.

Table 3 shows that anti-IgA antibodies were present in 26.3% (95% C.I. 10.1-51.4) of patients with selective IgA deficiency, however all patients with SLE had anti-IgA antibodies detected. Two of those patients had documented reactions to blood transfusions. As demonstrated in table 4, antinuclear antibodies were detected in a significant group of the patients with isolated

Table 3. Frequency of anti-IgA antibodies in patients with selective IgA deficiency (n = 38)

Diagnosis	# patients	# positive	%	95% CI
Selective IgA deficiency alone	19	5	26.3	10.1–51.4
IgA deficiency + Crohn's	6	2	33.3	6.0 – 75.9
IgA deficiency + SLE	5	5	100	46.2 - 100
IgA deficiency + ulcerative colitis	3	1	33.3	1.8 – 87.5
IgA deficiency + R.A.	2	1	50.0	2.7 – 97.3
IgA deficiency + scleroderma	1	1	100	5.5 – 100
IgA deficiency + + IgG subclass deficiency	2	0	0.0	-

Table 4. Frequency of antinuclear antibodies in patients with selective IgA deficiency (n = 38)

Diagnosis	# patients	# positive	%	95% CI
Selective IgA deficiency	19	11	57.9	34.0–78.9
IgA deficiency + Crohn's	6	2	33.3	6.0–75.9
IgA deficiency + SLE	5	5	100	46.3-100
IgA deficiency + ulcerative colitis	3	2	66.7	12.5–98.2
IgA deficiency + R.A.	2	1	50.0	2.7–97.3
IgA deficiency + scleroderma	1	1	100	5.5-100
IgA deficiency + IgG subclass deficiency	2	0	0.0	-

IgA deficiency (57.9%; 95% C.I. 34.0-78.9) and in all the patients with IgA deficiency and SLE.

A survey of ANA in the CVI group revealed that only 3 patients with CVI alone had a positive test; and neither of the two patients with CVI and SLE had a detectable titer. Patients with CVI and ITP had 50% positivity for ANA as seen in table 5.

Table 5. Frequency of antinuclear antibodies in patients with common variable immunodeficiency [CVI] (n = 33)

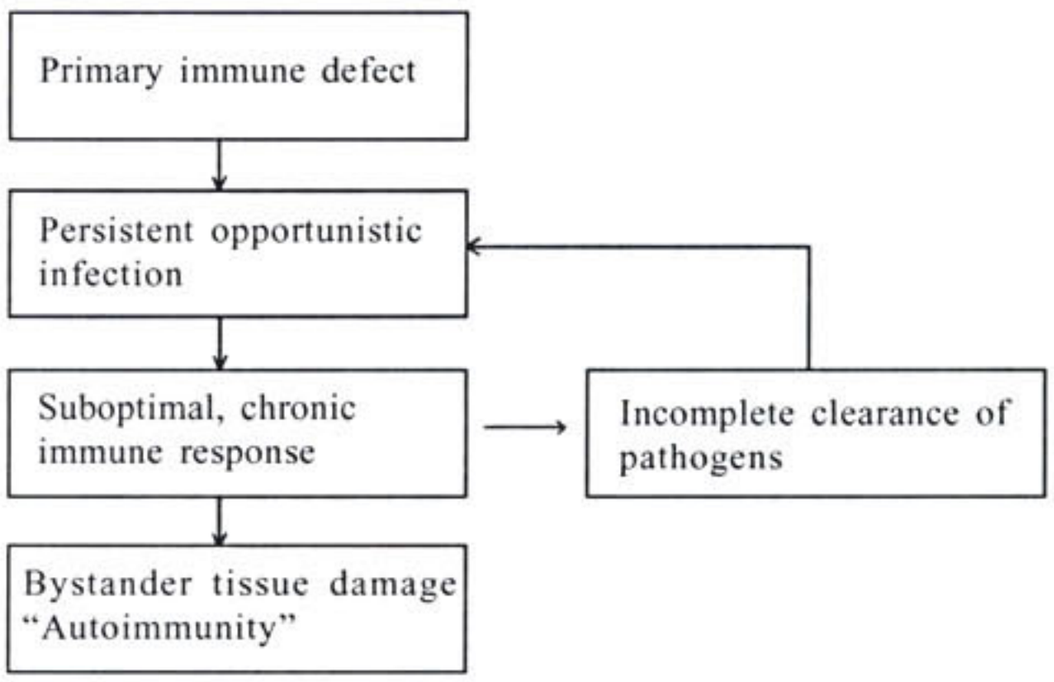
Diagnosis	# patients	# positive	%	95% CI
CVI alone	2	13	14.3	3.8–37.4
CVI + SLE	2	0	0.0	-
CVI + R.A.	1	0	0.0	-
CVI + Crohn's	3	0	0.0	-
CVI + hypothyroidism	1	0	0.0	-
CVI + ITP	4	2	50.0	9.2–90.8
CVI + AHA	1	1	100	5.5-100

Of the two patients with septic arthritis and CVI, Streptococcus pneumoniae was identified in one case and Haemophilus influenzae in the other. The aseptic arthritis patients with CVI had a mild course with mostly oligoarticular manifestations and minimal or no functional limitations.

Discussion

The presence of infections in patients with primary immunodeficiencies has allowed the association of autoimmunity with the inability of the host to eradicate the microbial pathogens and their antigens completely through the usual immune pathways. The result is a compensatory, often exaggerated and chronic inflammatory response by less effective alternative immune pathways, which damage not only infected cells but also surrounding tissue (figure 1). In this sense, autoimmunity in these patients does not result from a breakdown of tolerance to self-antigens but rather from tissue damage incurred as the host attempts to rid itself of foreign antigens (5).

Figure 1. Basis of autoimmunity in primary immunodeficiency diseases



In this study, the IgA-deficient group of patients had more representation of autoimmune conditions with a greater positivity for ANA as compared to the CVI group. Previous reports have indicated that 1-5% of IgA-deficient patients have SLE (6). Anti-IgA antibodies were present in 26.3% (95%, C.I. 10.1-51.4) of the IgA-deficient patients with no other conditions, whereas other reports mention 44% of positivity (7). A high prevalence of antinuclear antibodies not associated with any clinical autoimmune condition, as noted in the IgA-deficient patients in this study (57.9%; 95% C.I. 34.0-78.9), has prompted several theories to explain why IgA-deficient patients may have an increased risk of autoimmunity. Among these is that IgA on mucosal surfaces may bind to environmental antigens to promote their removal, and that persistence of environmental antigens (due to lack of IgA) leads to defective T cell regulation (8).

Inflammatory bowel disease (Crohn's disease and ulcerative colitis) has been reported in connection with IgA deficiency and CVI and taken together constitute the

most common clinical autoimmune presentation in both groups studied (9). ITP was the commonest organ-specific autoimmune condition identified in the CVI group, which is concordant with the experience in other groups (10). The organisms identified in the two patients with CVI and septic arthritis are among those usually encountered in B-cell immunodeficiency states. Contrary to a previous study by Cassidy, erosive arthritis was not observed (11). The limited number of patients studied does not allow a reliable estimate of the prevalence of SLE in the IgA-deficient population analyzed. It has been reported that SLE has a 20-30 times higher prevalence than in the normal population in IgA-deficient patients (12). Of note is the fact that three of the patients with IgA deficiency had relatives with systemic lupus erythematosus and two patients with IgA deficiency evolved to CVI.

The two cases with SLE later diagnosed as CVI pose a situation without an adequate explanation. In SLE, B cell activation prompts elevated autoantibody levels while CVI is characterized by deficient antibody production. Both patients were identified as CVI after more than five years of clinical SLE. Hypogammaglobulinemia has not been associated to SLE in the medical literature (13).

Despite the associations of autoimmunity and antibody deficiency syndromes, no specific genetic defect has been established as the presumed pathogenesis in either IgA deficiency or CVI (14). Observed differences in frequency of positive antibodies and clinical autoimmune conditions in our patients cannot be taken as typical due to the limited number examined and the exclusion of pediatric cases in the IgA deficient group.

A continued surveillance of these patients might help establish more definite tendencies regarding rheumatologic manifestations in primary immunodeficiencies.

Resumen

El objetivo de este estudio fue la caracterización de un grupo de pacientes con deficiencia selectiva de la inmunoglobulina A (IgA) e inmunodeficiencia común variable (ICV) en términos de su asociación a manifestaciones reumatológicas. A pesar que la base molecular de estos defectos ha sido ampliamente dilucidada, aún no ha sido posible explicar la frecuencia significativa conque están asociadas a desórdenes autoinmunes, además de los usuales problemas infecciosos. La dificultad simultánea para combatir infecciones (inmunodeficiencia) así como la capacidad del sistema inmunológico para producir reacciones en contra de los tejidos del propio organismo (autoinmunidad) constituye un enigma. En este estudio se evaluaron 71 pacientes con criterios diagnósticos de inmunodeficiencia selectiva de IgA (38 pacientes) e immunodeficiencia común variable (33 pacientes) para la detección de manifestaciones reumatológicas. Las condiciones autoinmunes más frecuentemente identificadas en los pacientes con inmunodeficiencia selectiva de IgA fueron la enfermedad de Crohn's y lupus eritematoso sistémico (SLE). Los pacientes con ICV manifestaron con más frecuencia purpura trombocitopénica immune (ITP) y la enfermedad de Crohn's. Se detectaron anticuerpos contra IgA en sólo 26.6% (95% C.I. 10.1-51.4) de los pacientes con deficiencia de IgA, pero en todos aquellos pacientes con SLE. El 50% de los pacientes con IVC y ITP presentaron positividad a anticuerpos antinucleares. En conclusión los pacientes con deficiencia de IgA en el estudio presentaron una prevalencia mayor de desórdenes autoimmunes y una más alta positividad a anticuerpos antinucleares al ser comparados con pacientes de ICV. La alta prevalencia de anticuerpos antinucleares encontrado en este estudio en pacientes con deficiencia de IgA y ninguna condición autoimmune asociada requiere ser evaluada en el futuro con miras a determinar por qué estos pacientes pueden estar a más alto riesgo de desarrollar desórdenes autoinmunes. La enfermedad de Crohn's y colitis ulcerosa fueron las manifestaciones autoinmunes más frecuentes en los dos grupos de patientes estudiados. ITP fue la condición autoimmune adscrita a un órgano más común identificada en el grupo con ICV, de forma similar a lo informado en la literatura. El reducido número de pacientes estudiado no permite hacer un estimado real de la prevalencia de SLE en el grupo de pacientes con deficiencia de IgA. Las diferencias observadas sobre la frecuencia de anticuerpos antinucleares positivos y las condiciones autoinmunes presentes en los pacientes evaluados no puede considerarse característica debido al tamaño de la muestra y la exclusión de pacientes pediátricos. La evaluación a largo plazo de la muestra estudiada puede ayudar a determinar la existencia de tendencias más definidas sobre la relación de manifestationes reumatológicas con las inmunodeficiencias primarias.

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