Selective immunoglobulin A deficiency: A retrospective study

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Abstract

The authors present a retrospective study of 82 IgA deficient patients (IgA < 5 mg/dl) followed in a Clinical Immunology Unit for a period of 15 years (1992-2006). The goal of this work is to evaluate the associated conditions and complications emerging from IgA-D.

The clinical symptoms in patients with IgA-D were recurrent infections (31.7%), autoimmune diseases (25.6%), allergies (24.3%), hematologic diseases (6.9%), endocrine diseases (4.87%) and oncologic diseases (7.3%). The respiratory system was the most affected by infections; systemic lupus erythematosus and rheumatoid arthritis were the most frequent autoimmune diseases; eczema and rhinitis were the most frequent allergic symptoms; gastric and colon adenocarcinoma were the most frequent oncologic diseases. Other disorders include Hashimoto´s thyroiditis, Diabetes Mellitus type 1, and idiopathic thrombocytopenia purpura, pernicious anemia and anaphylactic reaction to blood products.

IgA-D has a large clinical spectrum and an early diagnosis would indicate prophylaxis in patients with recurrent infections, autoimmune diseases and allergies. Patients with SIgA-D are at risk of developing a severe anaphylactic reaction upon receiving IgA-containing blood and blood products.

Key words: Selective Immunoglobulin A deficiency: retrospective study.

Introduction

IgA selective deficiency (IgA-D) is the most frequent of all primary immunodeficiencies. It is featured by a deficit on IgA production with low serial levels (< 5 mg/dL), and normal concentrations of IgM and IgG. It occurs with an average frequency of 1/700 Caucasian individuals,[1] being less frequent among Black and Asians.[2]

The cause of IgA-D is unknown. In some families there is evidence of transmission (a pattern of recessive or dominant autosomal inheritance was documented in some studies with IgA-D patients).[3] A possible IgA-D mechanism is blocking the differentiation of B lymphocytes expressing IgA at the surface. It is not clear whether this blockade occurs from an intrinsic change in lymphocytes B themselves, in the anomalous production of cytokines (growth factor, β-TGF transformer, interleukin 5) of lymphocytes T helpers or the lymphocytes B response to these cytokines.[3]

IgA immunodeficiency is increased in individuals with HLA antigens from class I and II: A1, A28, B8, B14, B40, DR3 and DR7, regardless of whether clinical symptoms are present.[3]

IgA reduced serial levels are associated to the use of medicines as Hydantoin, Sulphalazine and Penicillamine. Viral infections as intra-uterine rubella or an infection by Epstein-Barr virus and procedures as splenectomy or bone marrow transplant seem to be involved in IgA-D.[4]

Most individuals with IgA-D are healthy. Only 10% show a higher rate of infections, mainly respiratory ones. IgA-D is also higher in patients with serious hypersensivity reactions, autoimmune diseases,[5] and gastrointestinal and lymphatic malignant neoplasms[6], as Hodgkin´s disease.[7] It seems to exist also a link between chronic obstructive pulmonary disease and IgA-D.[8]

Project goal

This project general goal is, by means of a thorough clinic and laboratorial study, trying to understand better the selective IgA deficiency, namely in what concerns the factors triggering certain conditions. This project

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proposes to reach these goals revaluating patients with selective immunoglobulin A deficiency, based on the clinical history and the laboratorial study.

Clinical History

Current history, as well as personal and family background relevant for each case, considering the IgA relationship with certain diseases, namely:

- Rheumatoid diseases (systemic lupus erythematosus, rheumatoid arthritis, Still disease, mixed connective tissue disease, scleroderma, Sjögren´s syndrome, dermatomyositis and antiphospholipid syndrome);
- Endocrine diseases (Hashimoto thyroiditis, Graves´disease and diabetes mellitus type 1);
- Hematological diseases (Hemolytic anemia, pernicious anemia and idiopathic thrombocytopenic purpura);
- Gastrointestinal diseases (celiac disease, infections by Giardia lamblia, viral and autoimmune hepatitis);
- Atopic hypersensivity (rhinitis, eczema, angioedema, allergy to cow milk and allergic asthma);
- Chronic infectious diseases (namely of the respiratory, gastrointestinal and urinary tract);
- Malignant neoplasm diseases (colon adenocarcinoma, stomach malignant neoplasm, lymphomas, leukemia or other);
- Neurologic diseases, as myasthenia gravis.

Laboratorial evaluation

- The concentration of immunoglobulin A, G, M and D reflect lymphocytes B synthesis capacity, therefore to get their dosage is crucial in order to characterize IgA-D in general.[3]
- Search of systemic autoantibodies, because many conditions evolve with the presence of circulating immunocomplexes. There are reported links of selective IgA deficiency with complement synthesis impairment, therefore the assessment of these values was included in this study.[3]
- IgA deficiency has several cell implications, namely the presence of B populations unable to produce this immunoglobulin or changes in regulation and interaction T-B. The total number of lymphocytes and the differential counting of lymphocytes population was also evaluated.[3]

Materials and methods

82 patients over 18 years of age followed up at the Clinical Immunology Unit (UIC) of Santo Antonio General Hospital (HGSA), Porto, with selective deficiency of IgA, between 1992 to 2006 were retrospectively evaluated. The Clinical Immunology Service belongs to the Internal Medicine Department. The Clinical Immunology sector was developed at the core of Internal Medicine in the HGSA, propelled by the non existence of a Rheumatology and Infectiology Dept., and a special cooperation with the Immunology Laboratorial Service. Its assistance role is carried out with Outpatients, Admission and Group Consultation.

IgA-D diagnosis criteria were described by Amman and Hang in 1971. These criteria include patients with IgA levels less than 5 mg/dL, with normal IgM and IgG[9] and no risk of damaging the cell unit as happens with the usual tests.[10]

Patients underwent a clinical-laboratorial evaluation, according to the Organization standard procedures. Family history of allergy, immunodeficiency, recurrent infections, autoimmunity or consanguinity were investigated.

The dosage of immunoglobulin A, G and M was performed by kinetic immunonephelometry and immunoglobulin E by immunoenzymatic assay.[11] IgA-D diagnosis was considered when at least three dosages of IgA lower than 5 mg /dL were found.[1]

Dosing C_3 and C_4 was made by kinetic immunonepholometry. The evaluation of the complement hemolytic activity was made through a classic approach of red cell lysis.[12]

Systemic autoantibodies were searched by two approaches: PEG precipitation and subsequent determination on IgG precipitation and the evaluation of a complement source, which was mixed with the serum where one wanted to search for immunocomplexes.[13]

Cells study (lymphocytic subpopulations) in the peripheral blood correspond to the determination of the total number of lymphocytes and to differential count (by automatic counter) and to marking cells with monoclonal antibodies, and the enumeration (absolute and percentile) of cells with identified phenotypes was made by flow cytometry.[11,14]

Results

IgA deficiency diagnosis was established in 82 patients, from a total of 1147 patients coming from different medical areas (Clinical Immunology, Dermatology,

Internal Medicine, Hematology, Oncology, Allergology and Endocrinology). From a total, (54.8%) were from female patients and (45.2%) were from male patients. The age range was between 18 and 88 years of age, with an average of 43.8 years of age *(Fig.1)*.

The main causes to be referred to the Clinical Immunology Unit (UIC) were: recurrent infections (31.7%), rheumatologic autoimmune diseases (25.6%), allergies (24.3%), neoplasic diseases (7.3%), non neoplasic hematologic diseases (6.9%), endocrine diseases and (4.87%) liver diseases (2.43%) *(Fig. 2)*.

The most frequent infections were those of the respiratory tract (65%), tracheobronchitis and pneumonia representing (58.82%) and sinusitis (41.16%). Urinary tract infections accounted for (19.23%). Gastrointestinal tract infections represented (17.64%) *(Fig. 3)*.

The most frequent rheumatologic autoimmune diseases were: systemic erythematous lupus (47.61%) and rheumatoid arthritis (23.83%)*(Fig. 4)*.

The most frequent allergic manifestations were extrinsic asthma (50%) and allergic rhinitis (45% *(Fig. 5)*. A case of post-transfusion hypersensitivity was also identified.

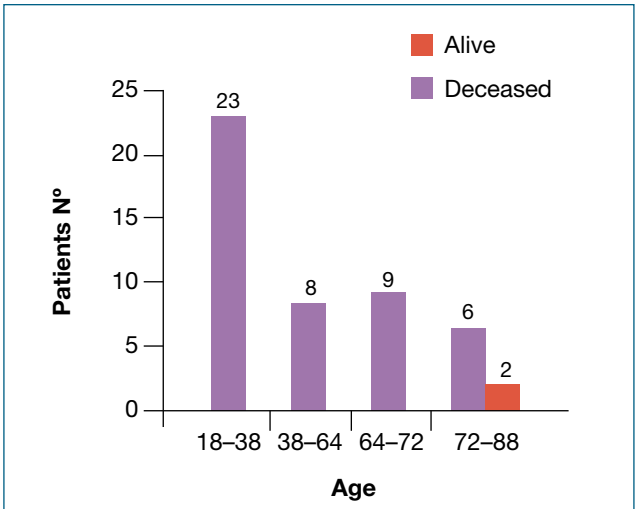
Among oncologic diseases, digestive neoplasm, namely gastric adenocarcinoma and colon adenocarcinoma, represented 2/3 of oncologic diseases followed by hematologic diseases of oncologic background, namely Hodgkin´s lymphoma and chronic lymphoid leukemia *(Fig. 6)*.

Other clinical manifestations were: chronic obstructive pulmonary disease (3.6%); non oncologic hematologic diseases, pernicious anemia (2.43%) and idiopathic thrombocytopenic purpura (1.21%); and endocrine diseases (4.87%), namely diabetes mellitus type 1 and Hashimoto thyroiditis.

Of all IgA-D patients, 18% showed IgG levels above normal, comparatively to the values of the same age in our average value. [3,15] The remaining immunologic tests to assess any change on cell immunity, complement or phagocytes, were normal in 65% of patients submitted to this study.

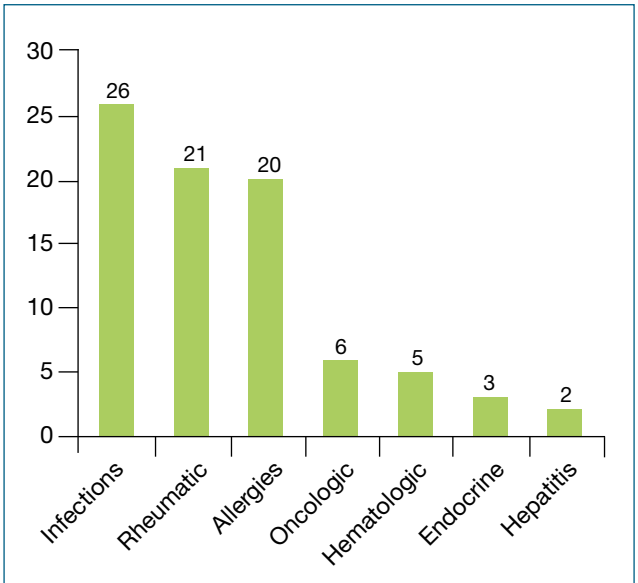
The presence of autoantibodies in the absence of associated clinical autoimmunity was detected namely: rheumatoid factor (4.5%) and nuclear antigens (18.2%).

There were patients with a family history of allergies (7.8%); and others with a history of autoimmune



IgA-D patients distribution by gender and age group.

FIG. 1

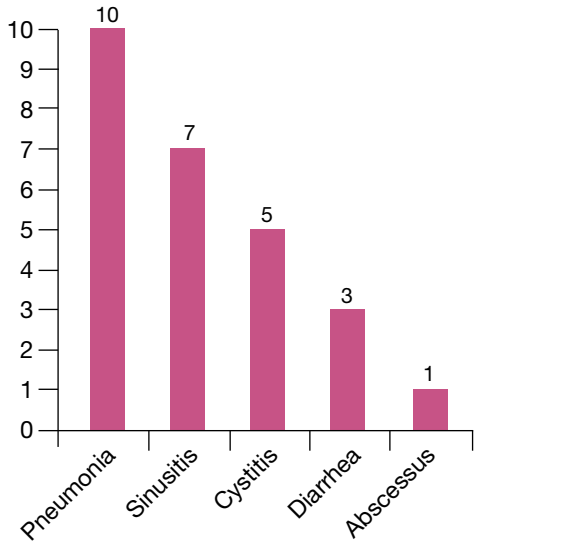


IgA-D patients distribution by associated conditions.

FIG. 2

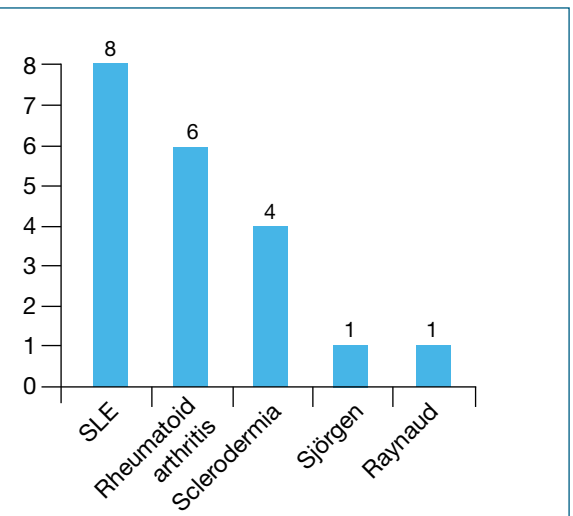
diseases with a rheumatologic background, namely rheumatoid arthritis (2.24%), although without associated IgA-D.

Regarding the deaths, a patient died due to community-acquired serious pneumonia at 88 years of age; the other one due to a metastatic adenocarcinoma at 54 years of age; and another one died in an old age setting in family surroundings.



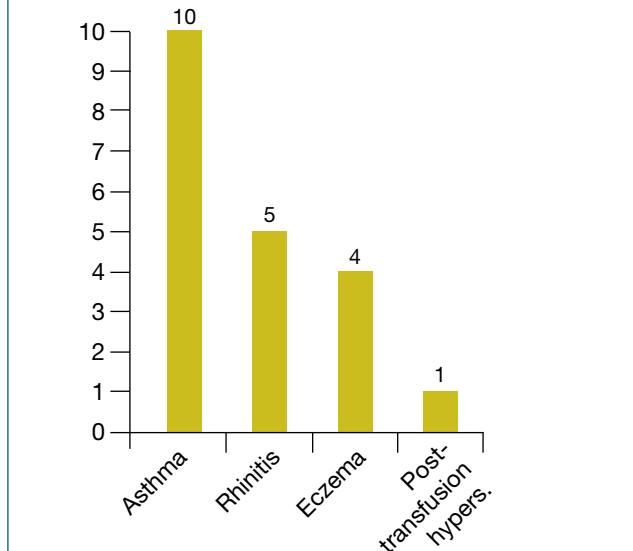
IgA-D and infections.

FIG. 3



IgA-D and rheumatoid diseases.

FIG. 4



IgA-D and allergic manifestations.

FIG. 5

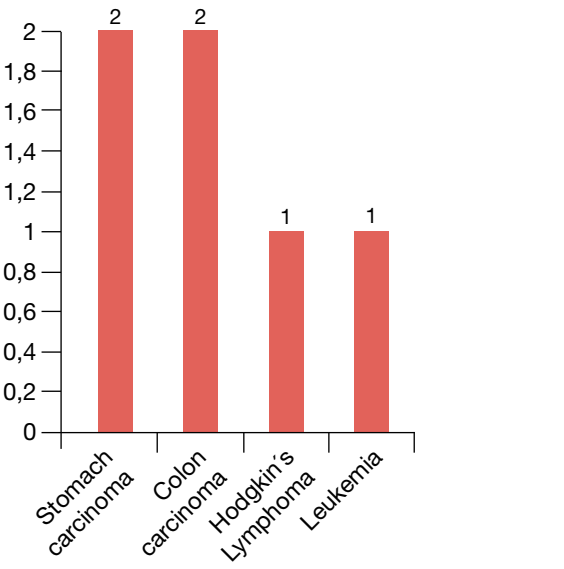
Discussion

IgA takes part in the local protection against pathogenic microorganisms in the mucosa surfaces and can reduce the uptake of inhaled or ingested antigens triggering an undesirable systemic response. Not much is known about the IgA role in the blood stream, presenting itself mainly in monomer form. [1]

IgA deficiency is the primary immunodeficiency more often followed at the Immunology Unit at Santo Antonio General Hospital. Globally, it reaches 1/700 Caucasian individuals, seldom occurring with Asian or Black people.[1] IgA-D prevalence in the male gender is higher than in the female gender, especially in symptomatic patients[14,15], while in the current study the female gender was prevalent. This outcome might be explained by Clinical Immunology Unit specificity, directed mainly towards the study of autoimmune pathology more frequent in the female gender.

The relative frequency of clinical manifestations associated to IgA-D, according to literature reports are infections (43%), allergies (20%), autoimmune diseases (14%), gastrointestinal dysfunctions (12%) and neoplasm (1%).[9] The main causes for assessment in our hospital were infectious conditions (31.7%), followed by autoimmune diseases of rheumatologic background (25.6%), allergies (24.3%), oncologic diseases (7.3%), endocrine diseases (4.87%) and non-oncologic hematologic diseases (6.97%). Again, the highest frequency of autoimmune diseases, can be explained by the Clinical Immunology Unit characteristics mentioned previously.

In patients studied, the respiratory tract infectious conditions were the most frequent, according to other



IgA-D and neoplasic diseases.

FIG. 6

authors reports[1]. 5 septicemia cases by community-acquired pneumonia and 2 cases of acute hepatitis B were seen. IgA-D is often associated with hepatitis C [1,2] although no case has been identified in this study.

Autoimmune diseases of rheumatologic background more commonly associated to IgA-D are rheumatoid arthritis and systemic erythematous lupus, which might occur from 7% to 36%.[16] In our study there was also a lupus (41.61%) and rheumatoid arthritis (23.83%) predominance.

IgA-D individuals seem to be at higher risk of developing neoplasm, mainly gastric and colon adenocarcinomas; cases of leukemia and Hodgkin´s lymphoma were also reported.[18] In the group undergoing a study, two cases of colon adenocarcinoma, two of stomach carcinoma a case of Hodgkin´s lymphoma and another of chronic lymphoid leukemia were identified.

Pernicious anemia was diagnosed in two patients. There is also a reported case of idiopathic thrombocytopenic purpura. The doubt remains whether this association is casual.[16]

In spite of reports regarding the association between autoimmune thyroiditis and IgA-D,[17] only two cases of Hashimoto thyroiditis were identified.

It was verified the relationship between allergic diseases and IgA-D.[18] Extrinsic asthma and allergies related with the upper airways were the conditions more often observed. It was also identified a case of post-transfusion hypersensitivity; there are studies linking IgA-D to anaphylactic shock in patients who have received blood transfusions.[19]

Some studies refer autosomal recessive patterns of inheritance and others relate autosomal dominant patterns of inheritance regarding IgA-D.[1] In this study, patients with a family history of allergy and autoimmune diseases, although without an IgA-D associated, were identified.

Immunoglobulins dosages, in the current study, have shown an increase on the IgG serum levels of 18%, probably triggered by infectious stimuli.

The presence of autoantibodies in the absence of associated clinical autoimmunity was detected in the serum of individuals with IgA-D, namely the rheumatoid factor and nuclear antigens in the percentile already shown. We do not know whether these patients are more prone to develop autoimmune diseases. Some studies say it is the case.[20]

The mortality rate was low (4.3%) in the IgA-D patients in the study. Deaths occurred due to septicemia, metastasized neoplasm or old age. IgA-D does not seem to have an influence on these conditions morbidity.

Conclusions

IgA-D is the most frequent primary immunodeficiency. It has a diversified clinical spectrum, and should be sought in patients with recurrent infections, allergic conditions or autoimmune diseases to indicate the early prophylaxis in infections conditions. IgA-D patients in need of blood transfusion, must be duly identified as they are at a higher risk of evolving to anaphylactic shock. ■

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