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Original article

Autoimmune diseases and autoantibodies in pediatric patients and their first-degree relatives with immunoglobulin A deficiency

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ABSTRACT

Introduction: Clinical manifestations of Immunoglobulin A Deficiency (IgAD) include recurrent infections, atopy and autoimmune diseases. However, to our knowledge, the concomitant evaluations of autoimmune diseases and auto antibodies in a cohort of IgAD patients with current age >10 years and their relatives have not been assessed.
Objectives: To evaluate autoimmune diseases and the presence of auto antibodies in IgAD patients and their first-degree relatives.
Methods: A cross-sectional study was performed in 34 IgAD patients (current age >10 years) and their first-degree relatives. All of them were followed at a tertiary Brazilian primary immunodeficiency center: 27 children/adolescents and 7 of their first-degree relatives with a late diagnosis of IgAD. Autoimmune diseases and autoantibodies (antinuclear antibodies, rheumatoid factor, and anti-thyroglobulin, anti-thyroperoxidase and IgA class anti-endomysial antibodies) were also assessed.
Results: Autoimmune diseases ($n = 14$) and/or autoantibodies ($n = 10$, four of them with isolated autoantibodies) were observed in 18/34 (53%) of the patients and their relatives. The most common autoimmune diseases found were thyroiditis (18%), chronic arthritis (12%) and celiac disease (6%). The most frequent autoantibodies were antinuclear antibodies (2%), anti-thyroglobulin and/or anti-thyroperoxidase (24%). No significant differences were observed in the female gender, age at diagnosis and current age in IgAD patients with and without autoimmune diseases and/or presence of auto antibodies ($p > 0.05$). The frequencies of primary immunodeficiencies in family, autoimmunity in family, atopy and recurrent infections were similar in both groups ($p > 0.05$).
Conclusion: Autoimmune diseases and auto antibodies were observed in IgAD patients during follow-up, reinforcing the necessity of a rigorous and continuous follow-up during adolescence and adulthood.

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Doenças autoimunes e autoanticorpos em pacientes pediátricos e seus parentes de primeiro grau com deficiência de imunoglobulina

Palavras-chave:
Deficiência de IgA
Autoimunidade
Autoanticorpos
Tireoidite

RESUMO

Introdução: As manifestações clínicas da deficiência de imunoglobulina A (DIgA) incluem infecções recorrentes, atopia e doenças autoimunes. No entanto, para o nosso conhecimento, as avaliações concomitantes de doenças autoimunes e autoanticorpos em uma coorte de pacientes com DIgA com idade atual > 10 anos e seus parentes não foram feitas.
Objetivos: Avaliar doenças autoimunes e presença de autoanticorpos em pacientes com DIgA e seus parentes de primeiro grau.
Métodos: Estudo transversal feito em 34 pacientes com DIgA (idade atual > 10 anos) e em seus parentes de primeiro grau. Todos foram acompanhados em um centro terciário brasileiro para imunodeficiência primária: 27 crianças/adolescentes e sete de seus parentes de primeiro grau com diagnóstico tardio de DIgA. Doenças autoimunes e autoanticorpos (anticorpos antinucleares, fator reumatoide e antitireoglobulina, antitiroperoxidase e anticorpos antiendomísio da classe IgA) também foram avaliadas.
Resultados: Doenças autoimunes (n = 14) e/ou autoanticorpos (n = 10, quatro deles com autoanticorpos isolados) foram observadas em 18/34 (53%) dos pacientes e seus parentes. As doenças autoimunes mais comuns encontradas foram tireoidite (18%), artrite crônica (12%) e doença celíaca (6%). Os autoanticorpos mais frequentes foram anticorpos antinucleares (2%), antitireoglobulina e/ou antitireoperoxidase (24%). Nenhuma diferença significativa foi observada no sexo feminino, idade no momento do diagnóstico e idade atual em pacientes com DIgA com e sem doenças autoimunes e/ou presença de autoanticorpos (p > 0,05). As frequências de imunodeficiência de primárias na família, autoimunidade em família, atopia e infecções recorrentes foram semelhantes em ambos os grupos (p> 0,05).
Conclusão: Doenças autoimunes e autoanticorpos foram observadas em pacientes com DIgA durante o acompanhamento, o que reforça a necessidade de um acompanhamento rigoroso e contínuo durante a adolescência e a idade adulta.

Introduction

IgA deficiency (IgAD) is the most frequent primary immunodeficiency (PID). It is a defect which is caused due to terminal B lymphocyte differentiation, resulting in an insufficient production of serum and secretory IgA (SIgA).[1–4] SIgA has some protective functions on mucosa, neutralizing microorganisms and proteins.[5–8]

The clinical manifestations of IgAD patients range from asymptomatic to recurrent infections, allergic symptoms and autoimmune diseases,[9] with an increased autoantibodies production.[10] Of note, autoimmune diseases occur in 7–36% of IgAD patients and autoantibodies are observed in more than 40% of the patients.[10,11] The prevalence of IgAD is 1–4% in systemic lupus erythematosus (SLE) patients,[10] 2–4% in rheumatoid arthritis (RA)[10] and 2.6% in celiac disease (CD).[12] Furthermore, autoimmune diseases are frequently reported in relatives of IgAD patients. Among the first-degree relatives of IgAD patients, 10% had autoimmune diseases compared to 5% in general population.[11–15]

However, to our knowledge, the concomitant evaluation of autoimmune diseases and auto antibodies in a cohort of IgAD patients with current age greater than 10 years and their relatives with IgAD has not been studied.

Therefore, the aim of this study was to evaluate the occurrence of autoimmune diseases and auto antibodies in a cohort of IgAD patients with current age greater than 10 years and their respective first-degree relatives followed at a tertiary Brazilian reference center for pediatric PID.

Patients and methods

We selected 126 IgAD patients followed at a Brazilian pediatric reference center for PID in the last 30 consecutive years. Ninety-two of the IgAD patients who were diagnosed at childhood had current age lower than 10 years and were excluded from this study. IgA assessment was systematically performed in all first-degree relatives that presented any symptoms or signals of recurrent infectious and autoimmune diseases, and IgAD diagnosis was established in 7/62 (11%) of first-degree relatives. Therefore, a cross-sectional study was carried out in 34 IgAD patients: 27 IgAD patients (current age greater than 10 years) and their 7 first-degree relatives with a late diagnosis of IgAD. The study was approved by the Ethical Committee and the written informed consent was obtained from all participants.

A systematic clinical evaluation was performed and included the assessments of various autoimmune disorders, recurrent infectious episodes, atopic manifestations and current or past neoplasia in the IgAD patients and their respective families. IgAD was diagnosed according to Pan-American Group for Immunodeficiency and European

Table 1 – Demographic data and clinical features in 34 IgA deficiency (IgAD) patients according to the presence of autoimmune diseases and/or auto-antibodies.

Variables	Autoimmune diseases and/or auto antibodies		p
	With (n = 18)	Without (n = 16)	
Demographic data			
Female	10 (56)	9 (56)	1.0
Age at IgAD diagnosis, yrs	8.9 (4–34)	13.7 (4–52)	0.25
Current age, yrs	19.8 (10–34)	19.6 (10–52)	0.98
Clinical features			
PID in family	9 (50)	8 (50)	1.0
Autoimmune diseases in family	2 (11)	3 (19)	0.65
Atopy	11 (61)	11 (69)	0.73
Recurrent infections	15 (83)	16 (100)	0.23

Results are presented in n (%) or median (range); PID, primary immunodeficiency.

Society for Immunodeficiency with exclusion of secondary IgAD.[16]

Juvenile idiopathic arthritis (JIA) was diagnosed according to International League of Associations for Rheumatology (ILAR) criteria.[17] Childhood-onset SLE (c-SLE) was diagnosed according to American College of Rheumatology criteria.[18] Ankylosing spondylitis (AS) was defined according to New York criteria.[19] Hypothyroidism was defined as reduced free thyroxine (T4) and elevated thyroid stimulating hormone (TSH) levels. Subclinical hypothyroidism was diagnosed as elevated TSH associated with normal T4. The presence of antithyroid antibodies was required to characterize autoimmune thyroiditis.[20] CD was characterized by at least four of the following findings: clinical manifestations (chronic diarrhea, stunting and/or iron deficiency anemia), positivity for CD IgA antibodies, HLA-DQ2 or DQ8 genotype, small intestine biopsy compatible with celiac enteropathy and response to gluten-free diet.[21]

Blood samples were collected from all IgAD patients and their relatives. Serum immunoglobulins (IgA, IgM and IgG) were measured by nephelometry (Behring Laser Nephelometer, USA) and the results were confirmed if they were positive. All patient samples were screened for antinuclear antibodies (ANA) by indirect immunofluorescence with HEp-2 cells (Euroimmun AG, Germany). Dilutions ≥1:80 were defined as positive. Rheumatoid factor (RF) was detected by immunonephelometry (Laborclin, Pinhais, Parana, Brazil, and reference value >8 IU/mL). The serum levels of TSH, free thyroxine (free T4), thyroglobulin, anti-thyroglobulin antibodies (anti-TG) and anti-thyroperoxidase antibodies (anti-TPO) were also determined. TSH and free T4 were measured by immunometric assays (Auto Delphia, Wallac Oy, Finland). The anti-TG and anti-TPO concentrations were determined using fluorescence enzymatic immunoassays (Auto Delphia, Wallac Oy, Finland; reference value >35 IU/mL). IgA class anti-endomysial (EMA) antibody of IgA isotype was evaluated by indirect immunofluorescence, using the umbilical cord as substrate (Dako, Copenhagen, Denmark; reference value >1:10).

Statistical analysis

Results were presented as mean ± standard deviation or median (range) for continuous and number (%) for categorical variables. Data were compared by *t*-test or Mann–Whitney test for continuous variables. Differences of categorical variables were assessed by Fisher's exact test. In all of the statistical tests, the level of significance was set at 5% ($p < 0.05$).

Results

Autoimmune diseases (n = 14) and/or autoantibodies (n = 10; four of them with isolated auto antibodies) were observed in 18/34 (53%) of patients and their relatives.

The most common autoimmune disorder was thyroid autoimmune disease in 6 (18%) of the IgAD subjects: hypothyroidism (n = 2), subclinical hypothyroidism (n = 2) and hyperthyroidism (n = 2). Four patients had chronic arthritis: three patients had JIA (persistent oligoarticular subtype) and the fourth patient had AS during adulthood. One patient had isolated haemolytic autoimmune anemia and the other patient had c-SLE with autoimmune thrombocytopenia. One patient and his sister had CD with an improvement after gluten-free diet.

Table 1 includes demographic data and clinical features in 34 IgAD patients and their first-degree relatives according to the presence of autoimmune diseases and/or autoantibodies. No significant differences were observed in the female gender, age at diagnosis and current age in IgAD patients with and without the presence of autoimmune diseases and/or of autoantibodies ($p > 0.05$). Likewise, the frequencies of PID and the presence of autoimmune diseases in family, atopy and recurrent infections were similar in both groups ($p > 0.05$) (Table 1). Upper respiratory tract infections were the most common findings, especially sinusitis (68%) and acute media otitis (58%).

Autoantibodies were observed in 10/34 (29%) of patients and their first-degree relatives (four of them had autoantibodies without autoimmune diseases). High serum titers of anti-TG and anti-TPO antibodies were observed in seven and five patients, respectively. One first-degree relative with CD had an ANA titer of 1:160 and one patient with c-SLE had an ANA titer of 1:320. In the patients without clinical autoimmune manifestations, two of them had positivity for both anti-TG and anti-TPO antibodies and the other two patients had only ANA positivity. Dense fine speckled patterns were

Table 2 – Demographic data and clinical features in 34 IgA deficiency (IgAD) patients according to presence of autoantibodies.

Variables	Autoantibodies		*p*
	With (*n* = 10)	Without (*n* = 24)	
Demographic data			
Female	7 (70)	12 (50)	0.45
Age at IgAD diagnosis, yrs	8.6 (4–30)	12.2 (4–52)	0.42
Current age, yrs	17.4 (12–30)	20.8 (10–52)	0.35
Clinical features			
PID in family	5 (50)	12 (50)	1.0
Autoimmune diseases in family	2 (20)	3 (13)	0.62
Atopy	6 (60)	16 (67)	0.71
Recurrent infections	9 (90)	22 (92)	1.0

Results are presented in *n* (%) or median (range); PID, primary immunodeficiency.

observed in ANA-HEp-2 cells of all patients. RF was absence in all IgAD subjects.

Demographic data and clinical features in 34 IgAD patients according to the presence of auto antibodies are shown in Table 2. Female gender, age at diagnosis and current age were similar in IgAD patients with and without the presence of auto antibodies ($p > 0.05$). PID and autoimmune diseases in family, atopy and recurrent infections were also comparable in both groups ($p > 0.05$, Table 2).

Discussion

Antibody deficiencies are the most common PID in our University Hospital, particularly IgAD.[22,23] The present study showed a high prevalence of autoimmune diseases and autoantibodies in IgAD patients followed-up at a tertiary teaching center.

Of note, various clinical manifestations may occur in IgAD patients, ranging from asymptomatic to recurrent infections, allergic symptoms and autoimmune diseases. The clinical spectrum probably depends on the association with antibody deficiencies, such as IgG2 subclass deficiency, specific antibody deficiency, mannose-binding lectin deficiency or common variable immunodeficiency.[24] Other possible pathogenesis is a compensatory mechanism, such as high salivary IgM and IgG.[25] In the present study, none of the IgAD patients had any other PID.

Autoimmune diseases occur more frequently in IgAD patients compared to healthy populations,[12,22] with the possibility of autoantibodies production, even without autoimmune clinical manifestations,[10,13] as observed herein. Both systemic and organ-specific autoimmune diseases have been described in association with IgAD[13] and the main autoimmune disorders associated with this immunodeficiency were: hypothyroidism, CD and rheumatic diseases.[9–13,26] Recently, IgAD has also been evidenced in 4% of our c-SLE population.[27]

Additionally, hematologic autoimmune disorders are very frequent in PID patients, especially antibody deficiencies, such as common variable immunodeficiency and IgAD, particularly idiopathic thrombocytopenic purpura and autoimmune haemolytic anemia, as evidenced in two of our IgAD patients.[28]

Importantly, the diagnosis of CD in IgAD patients may be very difficult, since the majority of the tests are based on specific IgA antibody. Therefore, it is important to measure the total serum IgA levels before the CD diagnosis.[29]

Regarding pathogenesis of autoimmunity in IgAD patients, the absence of IgA on mucosal surfaces induces absorption of many environmental antigens, such as diet proteins, and may provoke cross-reaction with self-antigens.[30,31] Moreover, the inability of defective immune response to handle these antigens may result in a compensatory response, thus leading to tissue damage and autoimmunity.[32,33] In addition, specific haplotypes (HLA-A1, HLA-B8 and HLA-DR3) were also found in IgAD patients associated with autoimmune diseases.[33]

Isolated ANA was also observed in our asymptomatic patients. Indeed, a Brazilian study showed that 12.6% of healthy children and adolescents in São Paulo had a positive ANA titer >1/80, without the presence of other autoantibodies. However, in this study IgA levels were not assessed.[34]

Auto antibodies were observed in 29% of our IgAD patients. This frequency was higher than our pediatric leprosy patients (16%)[35] and was lower than our c-SLE, juvenile dermatomyositis[36] and RASopathies[37] patients, who presented up to 93%, 59% and 52% of auto antibodies, respectively.

Another relevant result of the present study was the identification of IgAD in first-degree relatives, most of them asymptomatic, reinforcing the importance of PID evaluation in family members. Although many relatives had autoimmune diseases and mild infections, these manifestations were neglected by them and by physicians. Therefore, autoimmune diseases and infectious manifestations should be considered in the relatives with IgAD.

This study has limitations. These patients were referred to a tertiary university hospital, some of them with more complex diseases, which may have overestimated the autoimmune disorders in this group. Additionally, infants and children lower than 10 years, which is the most prevalent age group for this kind of PID, were excluded. A healthy control group was also not assessed.

In conclusion, a high prevalence of autoimmune diseases and autoantibodies was observed in IgAD patients, reinforcing the rigorous and continuous follow-up during adolescence and adulthood.

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Conflicts of interest

The authors declare no conflicts of interest.

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