ORIGINAL ARTICLE

Serum immunoglobulin a deficiency and autoimmune comorbidities: a crossectional study in 281 patients with systemic lupus erythematosus

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SUMMARY

OBJECTIVE: *To study the profile of associated autoimmune diseases in a series of patients with systemic lupus erythematosus (SLE) and see if such associations are linked to IgA deficiency.*

METHODS: *Two hundred eighty-one patients with SLE were studied for Ig A levels by nephelometry. Levels equal to or under 0.05g/dL were considered as IgA deficiency. Epidemiological and clinical data, including the presence of associated autoimmune diseases, were extracted from the patient's charts.*

RESULTS: *Ig A deficiency was found in 6% of the patients. In 30.2% of SLE patients, there was at least one more autoimmune disease; Hashimoto thyroiditis and Sjögren's syndrome were the most common. No association between the occurrence of associated autoimmune disease with IgA deficiency was found.*

CONCLUSIONS: *There is a high prevalence of autoimmune diseases associated with SLE. IgA deficiency does not affect the presence of these associations.*

KEYWORDS: *Lupus erythematosus, systemic. Immunoglobulin A. IgA deficiency. Autoimmune diseases. Hashimoto disease. Sjögren's syndrome.*

INTRODUCTION

The co-existence of more than one autoimmune disease in the same patient is a well-known clinical situation, although the reasons for this association are not fully explained. The existence of a shared genetic background that favors the rupture of immune tolerance is one of the hypotheses for this association[1]. Another reason proposed is the exposure to a common environmental trigger such as infections, drugs, pollutants[2,3], and even birth by cesarean section[4].

Autoimmune diseases (AID) are classified as systemic when the clinical profile reaches several tissues such as connective tissue diseases or organ-specific when a unique structure is affected[5]. Different combinations of these two types of situations are seen,

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generating an excessive burden on the patient. Chambers et al.[6] analyzed the association of systemic lupus with other AIDs and found that those with this association had more cumulative damage and higher mortality.

AIDs are considered to be more common in patients with immunoglobulin (Ig) A deficiency[7]. Ig A constitutes 15 to 20% of the total immunoglobulin pool in the body and it is primarily responsible for mucosal defense[8,9]. Ig A deficiency is one of the most common immune deficiencies, with a prevalence that shows variance according to the studied geographical area[9,10]. It is found in 1.96% of the general population in our region[11]. Autoimmune diseases linked to IgA deficiency are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), thyroiditis, and celiac disease, among others[8,12].

In the present study, we aimed to know the autoimmune diseases that co-occur in a cohort of SLE patients and if this association was higher in those with IgA deficiency.

METHODS

This study was approved by the local Research Ethics Committee, and the participants signed informed consent. We included 281 individuals with a diagnosis of SLE, older than 18 years, fulfilling at least 4 criteria of SLE classification from the American College of Rheumatology (ACR)[12,13]. This is a convenience sample that includes all patients from a single Rheumatology Unit that came for regular consultation for one year and agreed to participate in the study. Patients charts were reviewed for epidemiological, serological, and clinical data as well as diagnosis of associated autoimmune diseases.

The diagnosis of associated RA was done when the patient met six or more 2010 Classification Criteria for RA from the ACR/ EULAR (European League against Rheumatism)[13]; the diagnosis of scleroderma was considered when 9 or more points of 2013 ACR/ EULAR classification criteria for scleroderma were completed[14]. The American/European Classification Criteria for Sjogren's syndrome were used to perform the diagnosis of Sjögren's syndrome[15]; the Bohan and Peter[16] criteria for myositis and the 2006 Sydney criteria for antiphospholipid antibody (APS) syndrome[17]. The diagnosis of morphea, cutaneous polyarteritis nodosa (PAN), vitiligo, alopecia areata, and psoriasis was done by a dermatologist and/or skin biopsy. Hashimoto thyroiditis (HT) was diagnosed when the patient had hypothyroidism or goiter and the presence of anti-thyroperoxidase antibodies[18]. Celiac and Chron's disease required a compatible intestinal biopsy to be considered present. The diagnosis of type 1 diabetes mellitus (DM) was established by an endocrinologist, and of autoimmune hepatitis by a hepatologist. To perform the diagnosis of pernicious anemia, the patient needed to have histologically proven atrophic gastritis, megaloblastic anemia, cobalamin deficiency, and antibodies for intrinsic factor or anti-parietal cell[19]. Neuromyelitis Optica or Devic's disease was diagnosed when the patient had characteristic clinical manifestations in the presence of serum aquaporin (AQP)4-IgG positivity and/or specific neuroimaging findings[20].

Ig A measurement was done in venous blood by nephelometry; patients with 50 mg/dL or lower were considered IgA deficient[21]. At the moment of blood collection, none of the participants was using gold salts, sulphasalazine, D-penicillamine, or phenytoin nor had HIV or hepatitis C infection, which are situations known to be associated with acquired IgA deficiency[7].

Data were collected in frequency and contingency tables. Autoimmune disease frequency was expressed in percentage. Patients with and without IgA deficiency had their number of autoimmune diseases compared between themselves by Fisher and chi-squared tests. Numeric data (age at disease diagnosis) were compared by the Mann Whitney test. The adopted significance was 5%.

RESULTS

In the 281 studied patients, 262/281 (93.2%) were females; the median age was 43 years (Interquartile rate or IQR= 34-53 years), and the median disease duration was 36 months (IQR=12-72 months); 100/255 (39.2%) were auto-declared afro descendants and 155/255 (60.7%) were auto-declared Caucasians.

The co-occurrence of autoimmune diseases was seen in 85/281 (30.2%) of the cohort: 61/85 (72%) had an additional organ-specific AID, and 54/85 (64%) had an additional systemic AID. Twenty patients (24%) had additional organ-specific and systemic AIDs.

In 58/281 (20.6%) of SLE patients there was one more autoimmune disease; in 21/281 (7.4%) there were two others, and in 6/281 (2.1%) there were 3 or more associated diseases. The frequency of associated diseases is presented in Table 1.

In this cohort, 17/281 (6.0%) had IgA deficiency. The comparison of the epidemiological profile and prevalence of autoimmune diseases in patients with and without IgA deficiency is shown in Table 2.

DISCUSSION

We observed a high number of associations of AIDs, since almost 1/3 (30.2%) of the studied cohort had, at least, one more autoimmunity. Our results are very similar to those of Chambers et al.[6], who found a prevalence of 33% of additional autoimmune disease in a multiethnic cohort of SLE patients. The presence of two or more autoimmune diseases in the same individual is known as polyautoimmunity, while the coexistence of three or more is called multiple autoimmune syndrome (MAS)[22]. This aggregation of autoimmunity has been described as the kaleidoscope of autoimmunity by Weiss and Shoenfeld[23], who also observed familial aggregation of this phenomenon. Family history of autoimmune disease and female gender are considered to be risk factors of polyautoimmunity in general populations[24]. MAS has been detected in 8%-12% of cases of SLE according to a review by Matusiewicz et al.[22]. We found that SLE plus at least 2 more associated DAI, characterizing MAS, in 27/281 (9.6%) of our cohort.

In the present study, the most common association seen was with Hashimoto thyroiditis and Sjogren's syndrome, which appeared in 11.7% and 7.1%, respectively. The same profile was also observed by Rojas-Villarraga et al.[24], who studied 1,083 individuals with connective tissue diseases in general, including 335 with SLE.

Our studied series of patients with SLE had a high proportion of IgA deficiency (6.0%) when compared to a population of blood donors from our regions (1.96%). The hypotheses that have been used to explain this association are: (1)- since IgA is responsible for mucosal defense, an increased number of infections at these sites may offer antigens that can cross-react to auto-antigens by molecular mimicry[25,26]; (2)- a

TABLE 1. FREQUENCY OF ASSOCIATED AUTOIMMUNE DISEASES IN A COHORT OF 281 SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS.

Organ-specific autoimmune diseases		
	Number	%
Hashimoto thyroiditis	33/281	11.7%
Vitiligo	8/281	2.8%
Pernicious anemia	4/281	1.4%
Autoimmune hepatitis	3/281	1%
Morphea	3/281	1.0%
Psoriasis	3/281	1.0%
Neuromyelitis Optica (Devic's)	2/281	0.7%
Celiac disease	1/281	0.3%
Crohn disease	1/281	0.3%
Alopecia areata	1/281	0.3%
Diabetes mellitus I	1/281	0.3%
Cutaneous polyarteritis nodosa	1/281	0.3%
Systemic autoimmune diseases		
Sjogren's syndrome	20/281	7.1%
Antiphospholipid antibody syndrome	18/281	6.4%
Scleroderma	9/281	3.2%
Rheumatoid arthritis	6/281	2.1%
Dermatomyositis	1/281	0.3%

TABLE 2. COMPARISON OF EPIDEMIOLOGICAL PROFILE AND ASSOCIATED AUTOIMMUNE DISEASE IN PATIENTS WITH AND WITHOUT AUTOIMMUNE DISEASES IN A COHORT OF 281 SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS.

	With IgA deficiency N=17	Without IgA deficiency N=264	P
Median age at diagnosis (IQR)	25 (18-41)	29.0 (21.0-39.0)	0.76
Females (n)	17/17 – 100%	245/264 – 92.8%	0.61
Afrodescendants ethnic	6/15 – 40%	94/238 – 39.4%	0.96
Patients with associated DAI	7/17 – 41.1%	78/264 – 29.5%	0.31
Systemic DAI (n)	2/7 – 28.5%	48/78 – 61.5%	0.11
Organ-specific DAI (n)	7/7 – 100%	47/78 – 60.2%	0.12
Systemic + organ-specific DAI (n)	2/7 – 28.5%	17/78 = 21.7%	0.65
Hashimoto thyroiditis	2/17 – 11.7%	31/264 – 11.7%	1.0
Sjogren's syndrome	1/17 -5.8%	19/264 – 7.1%	1.0
Scleroderma	0	9/264 – 3.4%	0.61
Antiphospholipid antibody syndrome	1/17- 5.8%	17/264 – 6.4%	1.0
Vitiligo	1/17 – 5.8%	7/264 – 2.6%	0.39

DAI= Autoimmune disease; IQR= interquartile rate; n= number.

common genetic background, such as the presence of HLA A1-B8-DR3, may predispose to autoimmunity and immune deficiency[27]; (3)- an abnormal T cell regulation in individuals with IgA deficiency, mainly T regulatory cells, that also favor autoimmunity[25].

Although we found a high prevalence of SLE in IgA deficiency, we could not prove that IgA deficiency favored the association of autoimmune diseases in general nor facilitates a particular combination of them. Even after finding a high number of associations, it is necessary to observe that, in our study, the absolute number of a particular AID was low and the size of our cohort of individuals with lupus was relatively small (281 patients); it may not have had enough strength to prove such associations. So, the value of our data is primarily descriptive rather than comparative. This is a limitation of the present study. Studies with larger samples are necessary to clarify the role of Ig A deficiency in this context. Another limitation is not studying the SLE cumulative damage for comparison between those with and without association with DAIs. However, this study does highlight the high prevalence of associated DAI on SLE, warning clinicians to look for them in order to provide good care for the patient.

CONCLUSIONS

There was a high prevalence of associated AID in our cohort of SLE, with MAS appearing in 9.6% of patients. Hashimoto thyroiditis and Sjogren's syndrome were the most commonly seen. The presence of IgA deficiency did not favor the appearance of associations.

Author' contribution

Gustavo Felício Alexandroni Linzmeyer - Project conception, data collection, bibliographic review, draft; Fabiane Karen Miyake - Data collection, bibliographic review, draft; Thiago Alberto F. C. Gomes Dos Santos - Project conception, draft, review; Thelma L Skare - Project conception, statistical analysis, review.

Conflict of interest

None

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RESUMO

OBJETIVO: *Estudar o perfil de doenças autoimunes associadas em uma série de pacientes com lúpus eritematoso sistêmico (LES) e verificar se tais associações estão ligadas à deficiência de imunoglobulina (Ig) A.*

MÉTODOS: *Foram estudados 281 pacientes com LES para os níveis de IgA por nefelometria. Níveis iguais ou menores que 0,05 g/dL foram considerados como deficiência dessa imunoglobulina. Dados epidemiológicos e clínicos, incluindo a presença de doenças autoimunes associadas, foram extraídos dos prontuários dos pacientes.*

RESULTADOS: *A deficiência de IgA foi encontrada em 6% dos pacientes. Em 30,2% dos pacientes com LES encontrou-se a presença de, pelo menos, mais uma doença autoimune. Tireoidite de Hashimoto e síndrome de Sjögren foram as mais comuns. Não foi possível ligar a ocorrência de uma doença autoimune associada ao LES com deficiência de IgA.*

CONCLUSÕES: *Existe uma alta prevalência de doenças autoimunes associadas ao LES. A deficiência de IgA não afeta a presença dessas associações.*

PALAVRAS-CHAVE: *Lúpus eritematoso sistêmico. Imunoglobulina A. Deficiência de IgA. Doenças autoimunes. Doença de Hashimoto. Síndrome de Sjögren.*

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