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Original Article

Clinical and autoantibody profile in male and female patients with systemic lupus erythematosus: A retrospective study in 603 Brazilian patients

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Abstract

Objective: Sex and ethnic background may influence the clinical and autoantibody profile in systemic lupus erythematosus (SLE). This retrospective study aimed to compare the clinical and autoantibody profiles of male and female patients with SLE in a sample of Brazilian patients.

Methods: This was a retrospective study of 603 patients (48 males and 555 females) from a single rheumatology center. Collected clinical data included clinical findings according to the definition of 2012 Systemic Lupus International Collaborating Clinics classification criteria, the presence of antiphospholipid antibody syndrome according to the Sydney classification criteria and autoantibody profile (anti-dsDNA, anti-Ro, anti-La, anti-Sm, anti-RNP, rheumatoid factor, anticardiolipin [aCl] IgG, aCl IgM, lupus anticoagulant, and direct antiglobulin test), and histological results of kidney biopsies.

Results: It was found that females had higher age at disease onset (p=0.02), more oral ulcers (p=0.001), and presented more often with alopecia (p<0.0001) than males. Males had a higher prevalence of glomerulonephritis (OR=6.5; 95% CI=3.0-13.7) and anti-dsDNA (OR=2.59; 95% CI=1.38-4.85) than females, but no differences were found in the pattern of renal biopsies (p=0.46).

Conclusion: In this sample of Brazilian patients, the males had more renal involvement, fewer oral ulcers, and presented fewer times with alopecia than females.

Keywords: Systemic lupus erythematosus, sex, immunology

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that results from an interaction of genetic, hormonal, and environmental factors and has a very protean clinical profile (1-3). Its clinical and autoantibody profiles may be influenced by ethnicity, age at disease onset, and patient's sex (1).

SLE is more common in females with the reported female:male ratio from 8 to 15:1 in the reproductive years and with reduced proportion in the females at pre- and postmenopausal periods (1). However, it is possible that the under-recognition of this disease in males may affect this proportion (4).

Sex may also affect the clinical and autoantibody profile, but information on this relationship is controversial, varying according to the studied geographical region (1). A systematic review by Ress et al. (5) showed that male patients with SLE have an older peak age of incidence and prevalence than females. A multicentric study from Spain (4) that included 3,651 patients showed that males were diagnosed earlier than females, had more cardiovascular comorbidities, required more hospitalization, and had a higher mortality rate.

Knowing such differences may guide the clinician to establish prognosis and choose the best treatment in daily practice.

This study aimed to study a sample of Brazilian patients to understand the differences in clinical and autoantibody profiles between males and females.

Methods

This is a retrospective study approved by the local Committee of Ethics in Research of Sociedade Evangélica Beneficente de Curitiba, Brazil, under protocol 3.368.282 (Approval Date: June 25, 2018). It included patients with SLE from a single tertiary center followed-up during the period of 15 years who fulfilled at least 4 classification criteria of the 2012 Systemic Lupus International Collaborating Clinics (SLICC) (6).

Clinical data collection

Data on demographic, clinical, and serological profiles were obtained from the charts. The definition of all clinical findings followed those of 2012 SLICC classification criteria (6), and they were considered in a cumulative way. Antiphospholipid antibody syndrome was diagnosed according to 2006 Sydney criteria (7). Data on renal biopsy was obtained and classified according to the Renal Pathology Society/International Society of Nephrology (RPS/ISN) classification of lupus nephritis (8). All patients but those with class VI were classified according to the renal biopsy performed at the first episode of glomerulonephritis.

Serological collected data included levels of anti-dsDNA antibodies, anti-Ro/SS-A antibodies, anti-La/SS-B antibodies, anti-RNP antibodies, anti-Sm antibodies, anticardiolipin (aCl) IgG antibodies, aCl IgM antibodies, lupus anticoagulant (LA), rheumatoid factor, and direct Coombs. At our institution, levels of anti-Ro/SS-A antibodies, anti-La/SS-B antibodies, anti-RNP antibodies, anti-Sm antibodies, aCl IgG antibodies, and aCl IgM antibodies were estimated by ELISA (using Orgentec Kits®, Mainz, Germany), and levels of anti-dsDNA antibodies were measured by the immunofluorescence technique using *Crithidia luciliae* as a substrate. LA levels were estimated through a screening test, the dilute Russell viper venom test, and the test is performed by mixing patients' plasma with normal plasma and checking for coagulation using the Russell viper venom test. IgM rheumatoid factor levels were evaluated using a latex agglutination test (BioSystems S.A., Barcelona, Spain), and the direct antiglobulin test was performed using monoclonal anti-human globulin (Fresenius-Kabi-Brasil®, São Paulo, Brasil).

Statistical analysis

Distribution of numerical data was analyzed by the Shapiro-Wilk test, and central tendency was expressed in median and interquartile range. Nominal and categorical data were expressed in percentage (%).

Chi-squared and Fisher tests were used to compare male and female nominal data, and Mann-Whitney test was used for numeric data. The adopted significance was of 5%.

GraphPad Prism 6.0 software (GraphPad; San Diego, CA, USA) was used for all statistics analysis.

Main Points

- In a sample of Brazilian patients with SLE, males had more glomerulonephritis and anti-dsDNA autoantibodies and were younger at disease onset than females.
- Female patients had more mouth ulcers and alopecia than males.
- No differences were found in the histological pattern of renal biopsies according to sex.

Results

Description of studied data

A total of 603 patients were included: 48 males and 555 females with a female/male ratio of 11.5. Table 1 shows the prevalence of clinical and serological findings in this population.

In 235/247 patients with nephritis, data on histological classification according to the RPS/ISN classification (7) was available. Class II was present in 32/235 (13.6%), class III and III+V in 40/235 (17.0%), Class IV and IV+V in 93/235 (39.5%), class V in 46/235 (19.5%), and class VI in 24/235 (10.2%).

Comparison of clinical and serological profile between male and female patients with SLE

Table 2 shows the comparison of clinical and autoantibody profiles according to sex. In this table, it is possible to observe that male patients had disease onset at younger age, had more glomerulonephritis, and had more anti-dsDNA antibodies than females. Females had more mouth ulcers and presented more often with alopecia than males.

Table 3 shows the evaluation of kidney biopsies classification according to sex. No differences were found.

Discussion

Our results showed that, in our region, there is a ratio of 11 females for 1 male with SLE. This ratio has been found to be similar to those of a meta-analysis that included other 16 studies with patients with different ethnic backgrounds and had a prevalence of 9.3 females:1 male (8). The female pref-

Table 1. Clinical and serological profile of studied sample: 603 patients with systemic lupus erythematosus.

Features	n (%)
Median age at disease onset (years) (IQR)	29.0 (21.0-39.0)
Disease duration (months) (IQR)	24 (12-60)
Autodeclared afrodescendants (n)	195/501 (38.9)
Discoid lesions (n)	77/573 (13.4)
Photosensitivity	420/572 (73.4)
Malar rash (n)	310/558 (52.7)
Oral ulcers (n)	238/559 (42.5)
Alopecia (n)	281/516 (54.5)
Joint involvement (n)	454/585 (77.6)
Psychosis (n)	30/570 (5.2)
Seizures (n)	55/573 (9.6)
Serositis (n)	115/573 (20.1)
Hemolysis (n)	59/574 (10.3)
Leukopenia (n)	159/570 (27.8)
Lymphopenia (n)	93/557 (16.6)
Thrombocytopenia (n)	132/565 (23.3)
Glomerulonephritis (n)	247/579 (42.6)
Anti-Ro	221/549 (40.2)
Anti-La	103/548 (18.7)
Anti-dsDNA	227/557 (40.8)
Anti-Sm	137/532 (25.8)
Anti-RNP	157/498 (31.5)
aCl IgG	80/551 (14.5)
aCl IgM	74/548 (13.5)
LA	67/509 (13.1)
Direct antiglobulin test	64/471 (13.5)
AAF	12/470 (2.5)

IQR: interquartile range; aCl: anticardiolipin; LA: lupus anticoagulant; AAF: antiphospholipid antibody syndrome.

Table 2. Data on prevalence of clinical and serological findings in 603 patients with systemic lupus erythematosus and its comparison in male and female samples.

Features	Males (n=48)	Females (n=555)	p[a]
Median age at disease onset (years) (IQR)	23.5 (16.0-36.5)	30.0 (21.0-39.0)	0.02
Disease duration (months) (IQR)	24 (1-60)	26 (12-60)	0.56
Autodeclared afrodescendants (n)	21/43 (48.8%)	174/458 (37.9%)	0.19
Discoid lesions (n)	8/45 (17.7%)	69/528 (13.1%)	0.37
Photosensitivity (n)	27/44 (61.35)	393/528 (74.4%)	0.059
Malar rash (n)	22/45 (48.8%)	288/513 (56.1%)	0.34
Oral ulcers (n)	9/45 (20%)	229/514 (44.5%)	0.001[b]
Alopecia (n)	9/40 (22.5%)	272/476 (57.1%)	<0.0001[c]
Joint involvement (n)	32/48 (66.6%)	422/537 (78.5%)	0.057
Psychosis (n)	3/46 (6.5%)	27/524 (5.1%)	0.72
Seizures (n)	2/46 (4.3%)	53/527 (10.1%)	0.29
Serositis (n)	12/46 (26.1%)	103/527 (19.5%)	0.28
Hemolysis (n)	2/45 (4.4%)	57/529 (10.8%)	0.30
Leukopenia (n)	14/45 (31.1%)	145/525 (27.6%)	0.61
Lymphopenia (n)	9/42 (21.4%)	84/515 (16.3%)	0.39
Thrombocytopenia (n)	13/45 (28.8%)	119/520 (22.8%)	0.36
Glomerulonephritis (n)	38/47 (80.8%)	209/532 (39.3%)	<0.0001[d]
Anti-Ro (n)	13/45 (28.8%)	208/504 (41.2%)	0.10
Anti-La (n)	7/44 (15.9%)	96/504 (19.0%)	0.60
Anti-dsDNA (n)	28/45 (62.2%)	199/512 (38.9%)	0.002[e]
Anti-Sm (n)	14/42 (33.3%)	123/490 (25.1%)	0.24
Anti-RNP (n)	18/42 (42.9%)	139/456 (30.5%)	0.09
aCl IgG (n)	7/44 (15.9%)	73/507 (14.4%)	0.78
aCl IgM (n)	5/45 (11.1%)	69/503 (13.7%)	0.82
LA (n)	6/39 (15.3%)	61/470 (12.9%)	0.66
Direct anti-globulin test (n)	7/37 (18.9%)	57/434 (13.1%)	0.32
AAF (n)	1/38 (2.6%)	11/432 (2.5%)	1.00

[a]Chi-Square Test.
[b]OR=3.2; 95%CI=1.5-6.8.
[c]OR=4.5; 95%CI=2.1-9.8.
[d]OR=6.5; 95%CI= 3.0-13.7.
[e]OR=2.59; 95%CI=1.38-4.85.
IQR: interquartile range; aCl: anticardiolipin; LA: lupus anticoagulant; AAF: antiphospholipid antibody syndrome.

Table 3. Comparison of systemic lupus erythematosus glomerulonephritis classification in males and females.*

Glomerulonephritis classification	Males (n=37)	Females (n=198)	p
Class II	7 (18.9%)	25 (12.6%)	0.46
Class III and III+V	3 (8.1%)	37 (18.6%)	
Class IV and IV+V	17 (45.9%)	76 (38.3%)	
Class V	7 (18.9%)	39 (19.6%)	
Class VI	3 (8.1%)	21 (10.6%)	

*According to Renal Pathology Society/International Society of Nephrology classification.

erence for autoimmune diseases is a well-known phenomenon although not completely understood (9). Hormonal influence is one of the explanations. Estrogens seem to play a significant role in the female predisposition to this disease as they affect the development and function of the immune system increasing the production of T-helper 2 cytokines (9) and B cell expression (10). Other explanations are contact to antigenic stimulation in females during pregnancy (10) and the gene expression in the X chromosome (11). It has been documented that the number and genetic variants of X chromosome are associated with the risk of SLE development (12); on this chromosome, genes for toll-like receptor-7, interleukin-1-receptor-associated kinase 1, and the methyl-CpG-binding protein-2 are located (12).

Our results also pointed out that, in this sample, male patients with lupus had more glomerulonephritis, had more anti-dsDNA antibodies, and were younger at disease onset than female patients.

The literature has controversial data about high prevalence of glomerulonephritis in males, and the existing data on this feature show geographical variability. A comparative study of males and females with SLE from Asia, by Mok et al. (13), showed no significant differences in any major organ involvement. Another study, also in an Asiatic population, showed a trend toward more renal involvement in males (14). In the European population from Greece, diverse results have been found. One study showed that males had more serositis, but that the rate of renal involvement was considered similar in both sexes (15), while another pointed to higher nephropathy rate in males (16). A study, from Spain, failed to show differences in nephritis prevalence according to sex (17). Nevertheless, at least 2 studies from the USA (18, 19) and 1 from Latin America (20) showed that males had more nephritis than females. In this later study, by Molina et al. (20), a higher prevalence of anti-dsDNA antibodies in males was also found, as we did. This shows not only the great diversity of this disease according to patients' genetic background, but also the need to know the disease's clinical profile in the local population in order to correctly evaluate and treat patients with SLE.

In the current analysis, no differences in classes of glomerulonephritis were found. A study by Farah et al. (21), in Jordanian patients with SLE, showed sex-associated differences in the histological types of nephritis with less class IV and more class V in males. However, in this study, males had more nephritic syndrome and end-stage renal disease. Renau et al. (22) could not prove that sex influenced the renal outcome despite finding a trend toward a worse prognosis of glomerulonephritis in females. Unluckily, we have no data on the evolution of renal disease in our sample.

In this sample, alopecia and oral ulcers were more common in females, and a trend toward joint involvement and photosensitivity was observed. A decrease in musculoskeletal and mucocutaneous findings in male was found in several studies with patients of different ethnic backgrounds (13, 15, 18, 23). SLE mucocutaneous lupus lesions are typical and useful, raising this diagnosis possibility (24). Being less common in males, this diagnosis may not be so easily remembered, contributing to diagnosis delay in the male group.

An unexpected result in the present analysis was that female patients were older at disease onset than males. A review by Murphy and Isenberg (1) found similar age at disease onset, and Riveros-Frutos et al. (4) found earlier onset in females. One possible explanation for this finding is that the high prevalence of glomerulonephritis in males in the present sample—that prompts renal biopsy and the SLE diagnosis—may have contributed to an early recognition of the disease.

This study has several limitations. Not having data on the evolution of renal disease in either sex is one of them. The other is its retrospective design. Its main finding is the high prevalence of glomerulonephritis in males of our region. Renal involvement is one of the most serious and feared complications of SLE; rapid recognition and treatment are important to improve the outcome (25).

In conclusion, our sample of Brazilian patients with SLE showed that the male patients have more glomerulonephritis and anti-dsDNA antibodies and less presentations with alopecia and oral ulcers than females.

Ethics Committee Approval: Ethics committee approval was received for this study from the Committee of Ethics in Research of Sociedade Evangélica Beneficente de Curitiba, Brazil (Approval Date: June 25, 2018; Approval Number: 3.368.282).

Informed Consent: Informed consent was not obtained due to the nature of this study.

Peer-review: Externally peer-reviewed.

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