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Systemic Lupus Erythematosus in Males

A Study of 107 Latin American Patients

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Introduction

Systemic lupus erythematosus (SLE) is a clinically heterogeneous autoimmune disease of unknown etiology in which multiple factors play important roles. One of its most striking characteristics is the higher prevalence among young women (31, 41, 47), which suggests a key role of sex hormones (34). Sex distribution before puberty and late in life does not show the marked preponderance of females seen in early adulthood (9, 43, 45), and some family studies of SLE have shown a male predominance (17, 42). Additionally, the disease activity has been shown to be associated with pregnancy, the postpartum period, and occasionally the use of estrogen-containing oral contraceptives (37, 58, 63). Furthermore, the association of SLE in males with Klinefelter syndrome is well known (22, 23, 57, 61). On the other hand, androgens, antiestrogenic agents, danazol, and ovariectomy have been reported to have beneficial effects on disease activity (38, 52).

The obvious question is whether the disease manifests itself differently in males. Some investigators (6, 11, 12, 16, 21, 24, 28, 35, 39, 50, 59, 62, 65, 68, 69, 70, 71) claim that it does and that a much more aggressive course of the disease and a higher morbidity rate can be observed among male patients with SLE. In addition, differences in race and ethnicity may have a role in the expression of the disease (28, 31, 44, 51).

We undertook a cross-sectional study of 107 Latin American men from a series of 1,316 patients with SLE seen in 3 referral centers in Colombia and Mexico. The main purposes of the present study were to determine the clinical and laboratory features in our male SLE patients, and to compare them with those of our female SLE patients.

Patients and Methods

Patient population

This was a cross-sectional, multicenter, and binational study of 107 male patients with SLE compared with a group of 1,209 female patients with SLE who were treated and followed up in the rheumatology clinics of Hospital San Vicente de Paul, Universidad de Antioquia, and Clinica Leon XIII, Medellín, Colombia, and Instituto Nacional de la Nutrición Salvador Zubirán, Mexico City, Mexico, either as inpatients or outpatients between 1972 and 1993. Six hundred and forty-nine (49%) patients were seen in Colombia (73 males, 576 females) and 667 (51%) were seen in Mexico (34 males, 633 females). All patients met the American College of Rheumatology (ACR) revised criteria for the classification of SLE (67). None had drug-induced SLE. The age at diagnosis was the date at which an individual patient fulfilled at least 4 ACR criteria for SLE.

Clinical and laboratory manifestations

All relevant data on background, history, physical findings, and laboratory investigations of the patients were obtained from their medical records. The following clinical and laboratory manifestations of SLE were examined: 1) Arthritis: non-erosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion. 2) Joint deformity, chiefly pseudorheumatoid hand with swan neck deformities (Jaccoud-like arthritis). 3) Skin involvement. 4) Raynaud phenomenon. 5) Renal involvement: 5a) a positive renal biopsy result, 5b) active urinary sediment, or 5c) proteinuria >500 mg/24 h; nephrotic syndrome defined as >3.5 g of proteinuria in a 24-hour specimen or the presence of proteinuria (3+ to 4+) with a serum albumin level of

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Abbreviations used in this paper: ACR, American College of Rheumatology; SLE, systemic lupus erythematosus.

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<2.8 g/dL. 6) Neurologic involvement: 6a) seizures without other definable cause, or 6b) psychosis without other definable cause, or 6c) other condition such as peripheral neuropathy, stroke, transverse myelitis, chorea, or other CNS lesions directly attributable to SLE in the absence of other causes. 7) Pleuritis: pleural rub and/or effusion and/or typical pleuritic pain. 8) Pericarditis documented by electrocardiogram, rub, or evidence of pericardial effusion. 9) and 10) Arterial or venous thrombosis: diagnosed on clinical grounds and confirmed by complementary tests. 11) Autoimmune hemolytic anemia, with hematocrit <35% and reticulocyte count >4%. 12) Leukopenia, white cell count <4,000/mm^3. 13) Thrombocytopenia, platelet count <100,000/mm^3. 14) Antinuclear antibodies determined by indirect immunofluorescence using mouse liver or Hep-2 cells as substrate. 15) Anti-dsDNA antibodies determined with Farr's technique or by indirect immunofluorescence with *Crithidia luciliae* as substrate. 16–19) Precipitating antibodies to extractable nuclear antigens, including Sm, U1-RNP, Ro/SSA, and La/SSB, detected by double immunodiffusion. 20–22) Anticardiolipin antibodies of the IgG, IgM, and IgA isotypes measured by an ELISA method as described by Gharavi et al (26); 23) renal biopsies categorized according to the modified classification proposed by the World Health Organization (29).

Assessment of disease severity/organ damage

Disease severity in the 2 groups was examined under the following headings:

1) Number of patients with renal involvement,
2) Number of patients with permanent renal impairment (chronic renal failure—at least 2 samples with serum creatinine ≥ 2.8 mg/dL, 6 months apart, or dialysis requirement),
3) Number of patients with neurologic involvement,
4) Number of patients with severe cardiopulmonary involvement such as myocarditis, endocarditis, myocardial infarction, pneumonitis, pulmonary hypertension, alveolar hemorrhage,
5) Number of patients with osteonecrosis,
6) Number of patients who received >15 mg/day of prednisone,
7) Number of patients who received cytotoxic agents (mainly azathioprine and/or cyclophosphamide),
8) Number of patients who required dialysis,
9) Number of patients who underwent renal transplantation,
10) Mortality and causes of death.

Statistical analysis

Data are presented as mean ± standard error of mean and as percentages. Differences between means and proportions were established using the 2-tailed Mann-Whitney U-test, χ^2, or the Fisher exact test where appropriate, uncorrected for multiple comparisons. Statistical significance was set at alpha level ≤ 0.05.

Results

General characteristics

The entire cohort consisted of 1,316 patients: 107 (8.2%) men and 1,209 (91.8%) women (female:male ratio, 11:1). The mean age at the time of diagnosis was 26 years (range, 7–76 yr) for male patients and 28 years (range, 5–78 yr) for female patients. The interval between the time of onset and the diagnosis of SLE was 6 months in male and 8 months in female patients. No clinical signs of any disturbance in sexual development were observed in any patient, although neither sex hormone studies nor karyotypes were performed. There were no significant differences between Colombian and Mexican males except for the prevalence of alopecia which was more frequent in the Colombian group (56% versus 6%, $p < 0.0001$), and vascular thrombosis which was more frequent in the Mexican group (32% versus 11%, $p = 0.01$). Table 1 lists the main clinical findings from both groups.

Clinical and laboratory manifestations

Table 2 summarizes the prevalence of the main clinical findings observed in the patients at any time during the course of their disease. The 3 most common clinical features in males were arthritis, skin involvement, and renal disease, while in females these were arthritis, skin involvement, and Raynaud phenomenon. Renal involvement and vascular thrombosis were observed in male patients at a significantly higher rate than in female patients, while Raynaud phenomenon occurred less frequently. The occurrence of other clinical features did not differ significantly between the groups.

Table 3 lists the laboratory findings from our patients. Antinuclear antibodies were detected at some time during the course of the illness in all patients. The only statistically significant difference between the 2 groups was the presence of anti-dsDNA antibodies, which was higher in male than in female patients. The prevalence of other laboratory findings was similar in both groups.

TABLE 1. Main clinical findings in 107 Colombian and Mexican male patients with SLE

	Colombia (n = 73) %	Mexico (n = 34) %
Skin involvement	64	59
Alopecia	56*	6
Raynaud	30	24
Renal involvement	64	44
Seizures	15	6
Psychosis	4	3
Pleuritis	40	35
Pericarditis	16	15
Vascular thrombosis	11	32*
Hemolytic anemia	18	12
Thrombocytopenia	22	18
Leukopenia	40	32
Osteonecrosis	5	9
Anti-dsDNA	63	41
Prednisone ≥ 15 mg/day	90	100
Cytotoxics	33	41

* $p < 0.05$.
Abbreviations: SLE = systemic lupus erythematosus.

TABLE 2. Clinical manifestations in 1,316 male and female patients with SLE

	Men (n = 107) %	Women (n = 1,209) %	p Value
Arthritis	85	88	0.5
Jaccoud	6	5	0.6
Skin involvement	62	67	0.3
Raynaud	28	46	0.0002
Renal involvement	58	44	0.004
Seizures	12	11	0.7
Psychosis	4	8	0.1
Pleuritis	38	36	0.6
Pericarditis	16	13	0.4
Vascular thrombosis	18	11	0.03
Hemolytic anemia	16	11	0.1
Thrombocytopenia	21	20	0.8
Leukopenia	37	39	0.8

Assessment of disease severity/organ damage

The prevalence of renal disease (including nephrotic syndrome) and the need for moderate to high doses of prednisone (≥15 mg/day) was significantly higher in male than in female patients (Table 4). Moreover, the prevalence of neurologic involvement, osteonecrosis, and severe cardiopulmonary involvement and the need for cytotoxic agents, dialysis, and renal transplantation were higher in the male group, although the differences were not statistically significant. Mortality was also higher in the males, although the difference was not statistically significant. Ten men and 94 women died during the course of the study. Table 5 lists the causes of death in both groups. Males died more frequently from SLE-related complications (8/10), with lupus nephritis being the principal cause of death compared with the female group. Two of the 10 males died of infections (pulmonary tuberculosis and sepsis due to enterococcus).

Renal involvement was seen in 62 male (58%) and 527 female (44%) patients, with nephrotic syndrome seen more frequently in the male than female group (31% versus 22%, respectively, p = 0.04). The occurrence of chronic renal failure and the need for dialysis as well as renal transplantation tended to be more frequent in males, but the difference was not statistically significant. Renal histology was available for 351 SLE patients, 37 males and 314 females (51% versus 26%, respectively, p = 0.06). Table 6 outlines the prevalence of the different histologic manifestations. Diffuse proliferative glomerulonephritis was the most common pathologic feature in both groups.

TABLE 3. Serologic findings in male and female patients with SLE

	Men (n = 107) %	Women (n = 1,209) %	p Value
ANA	100	99	1
Anti-dsDNA	54	37	0.002
Anti-Sm	19	15	0.6
Anti-RNP	25	32	0.5
Anti-Ro/SSA	25	26	1
Anti-La/SSB	19	17	0.8
IgG aCL	27	31	0.7
IgM aCL	16	24	0.3
IgA aCL	19	22	1

Abbreviations: ANA = antinuclear antibodies.

TABLE 4. Variables of disease severity/organ damage in patients with SLE

	Men (n = 107) %	Women (n = 1,209) %	p Value
Renal involvement	58	44	0.004
Nephrotic syndrome	31	22	0.04
Chronic renal failure	11	9	0.5
Neurologic involvement	26	22	0.3
Cardiopulmonary involvement	21	16	0.2
Osteonecrosis	7	4	0.2
Prednisone ≥ 15 mg/day	93	85	0.01
Cytotoxics	36	28	0.09
Dialysis	11	6	0.1
Renal transplantation	6	4	0.5
Mortality	9.3	7.7	0.6

Discussion

Clinical studies have consistently demonstrated that females make up nearly 90% of all SLE cases, especially women of childbearing age. Men account for 4%-22% of most large series of patients with SLE (3, 14, 27, 32, 50, 55). In our study males were roughly 8% of the total cohort of lupus patients, with a female:male ratio of 11:1, a frequency similar to that observed by others (14, 27, 32, 55). The absence of significant differences between the 2 groups with

TABLE 5. Causes of death in 104 patients with SLE

	Men (n = 10) No. (%)	Women (n = 94) No. (%)
SLE-related	8 (80)*	37 (39)
Lupus nephritis	6*	15
CNS lupus	—	5
Cardiac	—	5
Pulmonary	1	8
Hemorrhage due to thrombocytopenia	1	1
GI vasculitis	—	2
Hepatic failure	—	1
Infection	2 (20)	24 (26)
Miscellaneous†/Unknown	—	33 (35)

* $p < 0.05$.

† Treatment complications, homicide, accidents, malignancy.

TABLE 6. Histologic findings in 351 renal biopsies

	Men (n = 37) %	Women (n = 314) %	p Value
Mesangial GN	11	5	0.1
Focal proliferative GN	5	8	1
Diffuse proliferative GN	59	60	0.7
Membranous GN	14	10	0.4
Sclerosis	11	17	0.6

Abbreviations: GN = glomerulonephritis.

regard to time intervals from disease onset to diagnosis suggests that there is no delay in diagnosis of the disease in males. The mean age at the time of diagnosis did not differ in the groups, although some authors have reported the onset of the disease in males at an older age (19, 32, 40, 65, 72).

Clinical manifestations

The prevalence of renal disease and vascular thrombosis was statistically higher in the male than the female group. In addition, the prevalence of CNS involvement, osteonecrosis, and severe cardiopulmonary involvement was higher in males, although the differences were not statistically significant. On the other hand, the prevalence of Raynaud phenomenon was lower in the male than the female group; similar findings were also observed (19) in Thai SLE patients.

Previous studies have noted gender-associated differences in a variety of individual clinical manifestations. For example, several investigators have found thrombocytopenia and autoimmune hemolytic anemia (4, 18, 39, 59, 64) as well as serositis (7, 14, 18, 46, 59, 64) to be more common in male lupus patients. In a review of 52 male lupus patients, Kaufman et al (39) found an increased prevalence of thrombocytopenia and renal disease without any other notable differences in clinical, laboratory, and serologic parameters. In a study by Miller et al (46) (51 males), pleuritis was more common in males compared with matched female lupus patients, while alopecia, photosensitivity, thrombocytopenia, and neurologic involvement were less common. In a review of 49 Israeli males, Sthoeger and colleagues (64) found a higher frequency of neurologic involvement, nephritis, thrombocytopenia, vasculitis, serositis, and hepatosplenomegaly in male SLE patients. Hochberg et al (32) noted no significant differences in the clinical and laboratory manifestations between 12 male and 138 female patients except for a higher prevalence of peripheral neuropathy in the male group. Ward and Studenski (72) compared 62 males with 299 females, and after adjusting for differences in age, race, and duration of follow-up, they found that male lupus patients had seizures more commonly and tended to progress to renal failure more often than females. Recently Koh et al (40) studied 61 Oriental males compared with 86 Oriental female SLE patients and found a lower prevalence of arthritis and leukopenia in males. The prevalence of the main clinical and laboratory manifestations of the most relevant series of males with SLE appears in Table 7.

TABLE 7. Main clinical and laboratory features in male patients with SLE, present and previous studies

	Present Study (n = 107) %	Ref. 14 (n = 92) %	Ref. 72 (n = 62) %	Ref. 40 (n = 61) %	Ref. 39 (n = 52) %	Ref. 46 (n = 51) %	Ref. 64 (n = 49) %
Arthritis	85	74	71	54	94	94	84
Malar rash	51	49	27	56	40	24	55
Discoid lupus	9	13	10	15	15	6	33
Raynaud	28	30	?	?	25	50	14
Nephritis	58	48	45	72	65	44	67
Neuropsychiatric	26	?	25	25	42	18	53
Pleuritis	38	72	65	8	33	72	41
Hemolytic anemia	16	25	42	10	13	8	?
Leukopenia	37	8	33	36	44	46	51
Thrombocytopenia	21	26	21	36	40	8	43
Anti-dsDNA	54	86	61	92	70	64	69
Anti-Sm	19	13	18	10	23	?	?
Anti-RNP	25	9	20	21	21	?	?
Anti-Ro	25	15	?	0	18	?	?
Anti-La	19	13	22	18	5	?	?
IgG aCL	27	21	?	?	?	?	?
IgM aCL	16	17	?	?	?	?	?
IgA aCL	19	?	?	?	?	?	?

Abbreviations: ? = data not provided; Ref. = reference number.

Serologic findings

In regard to serologic findings, the only statistically significant difference between male and female groups was the presence of anti-dsDNA antibodies, which was higher in males. This finding correlates well with the higher prevalence of renal disease seen in males, supporting the relationship between renal disease and anti-dsDNA antibodies (30). Fries and Holman (25) also found a higher prevalence of this autoantibody in males. Koh et al (40) found a lower prevalence of anti-Ro/SSA antibodies in Oriental males compared to females (21% versus 67%), a finding the Moutsopoulos group (21) reported previously. In our study, however, the prevalence of this autoantibody was 25% in males and 26% in females. Even though the prevalence of vascular thrombosis was higher in the male group, there were no significant differences in regard to the presence of anticardiolipin antibodies. Others (5, 54, 62) also have observed a higher prevalence of thrombotic events in male patients with lupus compared to female SLE patients, with or without anticardiolipin antibodies. Specker et al (62) found that 57% of the male SLE patients they studied experienced more than 30 thromboembolic events, in contrast to 9 events in 6% of the females ($p < 0.05$).

Renal disease

In agreement with most of the studies, we found a higher prevalence of renal disease in the male than the female group (58% versus 44%, respectively, $p = 0.004$), although the prevalence of chronic renal failure did not differ in the groups as the prevalence of diffuse proliferative lupus nephritis. Perhaps the most interesting and consistent finding in the analysis of gender differences in SLE is the demonstration of a higher prevalence of renal disease in male patients, in both the adult and pediatric population (11, 12, 16, 21, 24, 39, 50, 62, 69, 70), and a poorer survival rate. However, some studies do not support this view (14, 32, 40, 46, 53). The preponderance of female patients in nearly all SLE series has made it difficult to assess any gender difference in the severity of lupus nephritis. In addition to a higher prevalence of renal involvement, several studies point to a poorer renal outcome in male patients (6, 8, 12, 24, 35, 36, 49, 56, 68, 70). Baldwin and colleagues (8) found a higher prevalence of diffuse proliferative lupus nephritis in males. Moreover, Pollak and coworkers (56) found that 79% of males had active glomerular disease, compared with 49% of their female counterparts. Tateno et al (69) demonstrated that SLE in males was accompanied by more active nephritis, although it followed a benign course with therapy. Kaufman et al (39) found that 76% of 52 male lupus patients showed clinically active renal disease. Celermajer and colleagues (12) stated that 67% of young male subjects had diffuse proliferative lupus nephritis, in contrast to 22% of young female subjects. Wallace et al (70) found more nephritis and hypocomplementemia and a worse prognosis among male patients compared with female patients. Blum et al (11) reported the presence of renal failure in 47% of their male patients. Others (6, 24, 35, 72) have also suggested an increased risk of renal failure in males. For example, Austin and colleagues (6) noted male gender as a sign of poor prognosis in patients with lupus nephritis, and Ward and Studenski (72) showed an increased risk of renal failure in males. Iseki et al (35) analyzed 566 SLE patients (51 males, 9%); 51 lupus patients were considered to have end-stage lupus nephritis. The authors also found that male patients had significantly poorer renal survival with a significantly higher risk of developing end-stage lupus nephritis. Jonsson et al (36) also reported poorer renal survival among male SLE patients. The gender difference in renal survival (better outcome in females) was also seen in cases of idiopathic membranous glomerulopathy (20, 33).

Survival in male SLE patients also tends to be significantly lower than that reported for females (16, 24, 28, 39, 59, 65, 70, 71). Folomeev and Alekberova (24) analyzed the survival pattern in 120 Russian male patients with SLE and found that 27 (22.5%) patients died during the follow-up period, with end-stage lupus nephritis being the most common cause of death (63%). The survival at 5, 10, and 15 years was lower in the male group compared to female patients. Recently, Ward et al (71) analyzed the associations of some demographic factors with long-term survival (mean duration of follow-up, 11 years) in a cohort of 408 lupus patients, 69 of whom were males. They found that males had a higher total mortality rate than females, although SLE-related mortality rates did not differ by sex. In our study, we found that males had higher SLE-related mortality (especially due to renal involvement), although the total mortality did not differ by sex. These findings confirm that renal involvement is a major cause of morbidity and mortality in SLE patients (2, 27, 44, 48, 60, 70), particularly males.

Although our findings are similar to those from most studies, discrepancies with others most likely reflect different biases of ascertainment, including different ethnic and racial groups sampled, single versus multicenter studies, the small number of affected men in the various studies, primary versus tertiary referrals, and problems of ascertainment of clinical features. In an effort to contribute new data from Latin America, we have studied a very large population of SLE patients, perhaps one of the largest series of male lupus patients ever reported. Although they were recruited from 2 different geo-

graphic locations, both Hispanic populations share similar sociocultural, economic, behavioral, and health service utilization variables, which makes them suitable to be pooled under a single group. In addition, it should be emphasized that both populations of male lupus patients were almost clinically homogeneous since only 2 significant differences were found. Moreover, no major differences in the disease expression seem to occur among Hispanics with SLE from different Latin American countries (13, 15, 44). However, further immunogenetic studies are needed for a better definition of these populations. Although our design has limitations due to its retrospective fashion and cross-sectional nature, our findings support the overall conclusion that there are gender-associated differences in the clinical manifestations of SLE.

The reasons for this apparently gender-related variability in SLE expression are not well understood. It is likely that these differences are multifactorial in origin (1, 10, 41). Hormonal and other factors, including genetic and educational background and compliance, may explain these differences.

Summary

Clinical and laboratory features were analyzed in 107 Latin American male patients with systemic lupus erythematosus (SLE) who were compared with a group of 1,209 Latin American female patients with SLE to determine the presence of gender-associated differences. Males had an increased prevalence of renal disease, vascular thrombosis, and the presence of anti-dsDNA antibodies, as well as the use of moderate to high doses of corticosteroids, compared with female SLE patients. Although there was no difference in mortality from all causes, SLE-related mortality was higher in the male group. All these findings are consistent with a more severe disease in Latin American males than in female patients from the same region.

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