Systemic Lupus Erythematosus Disease Severity in Men and Women: A Case-Control Study

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ABSTRACT. ***Objective.*** To assess the severity of systemic lupus erythematosus (SLE) in men compared to women.

Methods. A validated Lupus Severity of Disease Index (SDI) was used to assess disease severity in a retrospective multicenter case-control study. Each man (n = 18) was matched with 1–3 women (n = 36) for age, disease duration, and clinical setting. Clinical and serologic features were assessed and compared.

Results. There was no significant sex difference in disease severity (SDI 4.8 men vs 3.9 women). Comparison of other clinical or serologic manifestations showed that cerebritis, thromboembolic phenomena, and antiphospholipid antibodies were more common in men.

Conclusion. There is no difference in lupus disease severity between men and women. However, there are sex-specific differences in expression of some disease manifestations. (J Rheumatol 2002; 29:1674–7)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS MALES DISEASE SEVERITY

Systemic lupus erythematosus (SLE) is a disease affecting both women and men. A female predominance is clearly evident as men are a minority, 4–22% of lupus populations[1–3]. These male patients have been extensively studied and compared to their female counterparts, but no consistent differences have emerged. Survival rates of men have been shown to be worse[4-8], better[9,10], and comparable[11-14] to survival rates of women.

Disease severity is an outcome that reflects the cumulative disease activity over time as well as the predilection for major organ involvement (e.g., nephritis, cerebritis). Because of the conflicting results in other studies, we assessed disease severity in male and female patients with lupus using a validated index, the Severity of Disease Index (SDI)[15] (Table 1) in a retrospective case-control study. We also determined if there were sex differences for clinical, serologic, or therapeutic features of SLE.

MATERIALS AND METHODS

The charts of all living male patients followed until January 1994 at New York Medical College, Valhalla, NY, or Montefiore Hospital Medical Center, Bronx, NY, meeting American College of Rheumatology (ACR) criteria for SLE[16] were identified for study. Both these centers have an interest in lupus and have established outpatient clinics dedicated to the care of patients with lupus. Careful records are kept on all clinic as well as private patients. Male subjects were identified from the investigators' files. All living female patients followed at the 2 centers meeting the ACR criteria for SLE were screened for age, disease duration, and clinical setting (clinic or private practice) as a proxy for socioeconomic status (SES). Within each center each man was matched with 1–3 female patients for age (± 5 years), disease duration (± 1 year), and clinical setting. In a cross sectional analysis, all available inpatient and outpatient records of these men and women were examined. There was no apparent difference between men and women in the amount of information available for review. A data collection form was utilized to record the variables of interest for each patient. The SDI, a cumulative score of clinical and laboratory variables, was determined for each patient. Its components are clear and easily identifiable. The SDI has been validated and shown to correlate with physician's global assessment of severity, renal histologic chronicity, and serum albumin[15]. The presence of other clinical features such as Raynaud's phenomenon, alopecia, deep venous or arterial thrombosis, vasculitis, clinically significant avascular necrosis, or major infections was recorded for each patient. The serologic variables of interest included anti-Ro, La, RNP, and anticardiolipin antibodies (aCL: IgG, IgM, or IgA). Therapeutic features such as the administration of > 30 mg/day prednisone (or equivalent), the use of pulse intravenous corticosteroids, hydroxychloroquine, azathioprine or cyclophosphamide were also assessed as categorical variables.

Data were analyzed by Student t test for comparison of the mean SDI and the paired t test for comparison of the SDI within each matched set. Sample size calculations with uneven numbers per group set at a power of 80% revealed that 16 men (matched to 32 women) would be required to detect a significant mean SDI difference between men and women of 2, while 62 men with 124 women would be required to detect a mean SDI difference of 1. Odds ratios (OR) were determined for clinical and laboratory features to determine the potential risk/likelihood that a particular variable was associated with male status.

RESULTS

Twenty-five male patients were initially identified at the 2 centers. Seven men could not be included for further

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Table 1. The Lupus Severity Index[15].

1 point	
	Lowest recorded hematocrit to date: 30–37%
	History of proteinuria (2+ or more)
	Highest recorded creatinine to date: 1.3–3
	4–6 ACR criteria for SLE satisfied to date[16]
2 points	
	History of cerebritis (seizure or organic brain syndrome)
	History of pulmonary disease (lupus pneumonitis, pulmonary hemorrhage, or pulmonary hypertension)
	Lowest recorded hematocrit to date < 30%
	Highest recorded creatinine to date > 3
	Biopsy proven diffuse proliferative glomerulonephritis
	7 or more ACR criteria for SLE satisfied to date[16]

analysis as there were no appropriate female controls that matched by age, disease duration, and clinical setting. The 7 men who were subsequently excluded from further analysis were different from the population studied further; they were older [mean age 50.0 ± 21.2 yrs (1 SD)], were predominantly Caucasian [86%, 6 patients; one man (14%) was Black], and were followed in a private practice setting (86%, 6 patients). Additionally, they had a shorter followup interval than the group that we continued to study; the mean disease duration of the 7 excluded males was 4.7 ± 5.7 years. Of the 18 men who were examined further, 7 matched 1:1, 4 matched 1:2, and 7 matched 1:3. Characteristics of these men and women are shown in Table 2. Since the studied groups were matched for age, disease duration, and clinical setting, as expected, there were no significant differences between men and women for these variables. The population had a mean age of about 37 years and the diagnosis of SLE had been made roughly 10 years earlier. The mean male SDI (4.8 ± 2.60, 1 SD) was not significantly different from the mean female SDI (3.9 ± 2.10, 1 SD) ($p > 0.05$). Furthermore the mean difference in SDI of the matched sets was 1.5 ($p > 0.05$). The frequencies of clinical, serologic, and therapeutic features are shown in Table 3. Significant differences between male and female patients were seen for cerebritis (OR 13.5, 95% CI 1.4, 126.4) and deep venous or arterial thrombosis or pulmonary emboli (OR 6.5, 95% CI 1.1, 38.0). Men were also 4.4 times (95% CI 1.3, 14.8) more likely to have a positive aCL than women. There was no statistical difference between men and women in the prevalence of antibodies to Ro and La antigens, the use of hydroxychloroquine, azathioprine, cyclophosphamide, high dose or pulse intravenous corticosteroids, or the frequency of major complications such as infection and symptomatic avascular necrosis.

Table 2. Patient demographics.

	Male	Female
N	18	36
Age, mean ± 1 SD, yrs	37.3 ± 10	37.6 ± 10
Disease duration, mean ± 1 SD, yrs	10.5 ± 7.4	9.6 ± 6.4
Percentage followed in clinic setting (n)	67 (12)	78 (28)
Ethnic origin, % (n)		
Caucasian	50 (9)	42 (15)
Black	17 (3)	19 (7)
Hispanic	28 (5)	36 (13)
Other	5 (1)	3 (1)

DISCUSSION

The etiology of SLE is multifactorial. A major risk factor for the development of SLE is female sex. The prevalence ratio of female to male at age of onset of disease rises from about 2:1 as patients reach puberty to peak in young adulthood at 8:1, and then declines in the 6th decade, concurrent with the onset of menopause[17].

We examined the severity of disease as well as clinical features and serologic tests in men and women with lupus. We used the SDI, a validated measure of lupus disease severity with a case-control design to match and control for nondisease factors that might affect severity. Younger age and lower SES are associated with poorer longterm prognosis and perhaps more severe disease[5,18-21]. The severity of an illness may also be a function of its duration. Since we were interested in determining whether sex affected disease severity, we controlled for these other factors by matching men and women with respect to age, clinical practice setting (as a proxy for SES), and disease duration.

Gladman and colleagues have proposed the use of a damage index as an alternative outcomes measure for clinical epidemiologic studies[22]. The damage index measures total disease burden by quantifying the irreversible effects of both active disease and the complications of its treatment over time. This differs from a severity index, which does not look at effects of treatment, but rather scores the effects of active disease over time and is a record of these events (not necessarily irreversible) over the course of a patient's illness; an activity index is a snapshot at one moment in time. A severity index may be more useful for determining whether men and women have similar or different diseases and by inference, similar or different etiologies and modulating factors. The SDI of men with lupus was not significantly different from the SDI of women with lupus. Further, comparison of other measurements that might reflect disease severity, such as treatment factors or complications of treatment, again revealed no significant differences between men and women.

Our study is limited by both its retrospective nature and the small number of male subjects. A prospective cohort of lupus patients entered at disease onset (an inception cohort) would be the ideal population to examine the question of sex differences in disease severity. A prospective study would additionally limit the selection bias created by examination of living patients (both male and female). However, the low incidence of lupus in the general population, as well as its

Table 3. Features of SLE in men and women.

	Male	Female	Significant OR (95% CI)
N	18	36	
SDI ± 1 SD	4.8 ± 2.6	3.9 ± 2.1	
Clinical features, % (N)			
Lowest hematocrit 30–37%*	44 (8)	47 (17)	
Lowest hematocrit < 30%*	28 (5)	33 (12)	
Proteinuria (2+ or more)*	78 (14)	53 (19)	
Highest creatinine 1.3–3*	39 (7)	25 (9)	
Highest creatinine > 3*	11 (2)	6 (2)	
Cerebritis*	28 (5)	3 (1)	13.5 (1.4, 126.4)
Pulmonary disease*	11 (2)	3 (1)	
DPGN*	17 (3)	22 (8)	
Raynaud's	44 (8)	47 (17)	
DVT/PE	28 (5)	6 (2)	6.5 (1.1, 38.0)
Alopecia	44 (8)	47 (17)	
Vasculitis	33 (6)	17 (6)	
4–6 ACR criteria*[16]	61 (11)	78 (28)	
≥ 7 ACR criteria*	39 (7)	19 (7)	
Serologic results, % (N)			
Anticardiolipin	56 (10)	31 (11)	4.4 (1.3, 14.8)
Anti-Ro	11 (2)	31 (11)	
Anti-La	11 (2)	11 (4)	
Anti-RNP	11 (2)	25 (9)	
Therapy and complications, % (N)			
Prednisone ≥ 30 mg/day	78 (14)	83 (30)	
Hydroxychloroquine	33 (6)	47 (17)	
Azathioprine	56 (10)	42 (15)	
Cyclophosphamide	17 (3)	22 (8)	
Opportunistic infection	22 (4)	17 (6)	
AVN	17 (3)	11 (4)	

* Criteria for Severity of Disease Index[15]. DPGN: diffuse proliferative glomerulonephritis, DVT/PE: deep veinous thrombosis/pulmonary embolism, AVN: avascular necrosis.

female predominance, makes such a longitudinal study difficult to accomplish. We have attempted to take the retrospective aspect of this study into consideration by matching men and women on disease duration. We recognize that we cannot totally exclude a type II error affecting our result showing no statistical difference in disease severity between men and women. However, the difference between the mean severity scores of men and women is less than 1, suggesting no clinically relevant difference. Further, since multiple comparisons were made as we looked at a number of disease manifestations, our finding that men and women differ significantly in the expression of cerebritis, thrombosis, and aCL should also be tempered by the possibility that this finding may in part be due to chance.

A review of the many studies that compare the prevalence of various clinical and serologic features in male and female lupus reveals that there are no consistent differences and occasional contradictions among reports. For example, several investigators have reported an increased frequency of renal involvement in male lupus[9,14,23-27], while one study reported a decreased prevalence of diffuse proliferative glomerulonephritis[28]. Significant sex differences for neurologic features have been described and include a greater prevalence in males of peripheral neuropathy[29] or seizures[30], as well as a lower prevalence in men of psychosis[28] or neurologic involvement[31]. Other sporadic significant findings include a reduced prevalence in men of arthritis[32,33], alopecia[9,27,31], Raynaud's[27], fibrositis[9], photosensitivity[31], thrombocytopenia[31], and leukopenia[32] and an increased frequency in men of serositis[14,31,34] or skin disease[35]. There is no clear explanation to account for these differences of clinical and laboratory manifestations. One possibility is that there are inherent differences between lupus cohorts. Another explanation relates to the 30 year time span over which these studies have been published. With increased awareness of SLE and shorter intervals between the onset of symptoms, diagnosis, and initiation of treatment, there is improved control of inflammatory manifestations that may result in changes of disease expression over time. We controlled for this factor by matching male lupus patients to female patients by age and disease duration. Our data indicate that men have more cerebritis (psychosis or seizure) than women. In addition, there is a higher incidence of thrombotic events and aCL. Other reports have observed no

differences between men and women in the prevalence of antiphospholipid antibodies, anticardiolipin[33], false positive VDRL[28,30-32], or elevated coagulation times[28,31], while one recent abstract reported that men with SLE were more likely to have a lupus anticoagulant (but not an aCL) and thrombosis[36]. We found not only a higher prevalence of aCL but additionally noted an increased rate of thrombotic events in men compared to women with lupus. The etiology of these observations is not known and merits future investigation.

Although men and women with lupus exhibit no sex difference in disease severity they do express different disease manifestations, with increased frequency of cerebritis, vascular thrombosis, and anticardiolipin antibodies. Men with lupus should be routinely tested for antiphospholipid antibodies and monitored for thrombotic events.

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