International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2014; **17:** 394–399

ORIGINAL ARTICLE

Clinical and immunological pattern of systemic lupus erythematosus in men in a cohort of 2355 patients

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Abstract

Aim: To investigate the impact of gender on expression of systemic lupus erythematosus (SLE) in a cohort of 2355 SLE patients as one of the largest series of cases among the present reports.

Method: In this retrospective study we used medical records of all patients (239 male and 2116 female) of the SLE registry of Rheumatology Research Center (RRC), Tehran University of Medical science (TUMS), Iran. Both clinical and paraclinical manifestations of SLE patients have been registered in this database since 1976 and updated during their follow-up. Chi-square test was used to compare the clinical and paraclinical manifestations in men and women at disease onset and during the disease course. We used logistic regression to compute odds ratios with 95% confidence intervals. A P-value < 0.05 was considered as statistically significant.

Results: Mean age at disease onset was 25 ± 11.8 and 24.5 ± 10.3 years in men and women, respectively ($P = 0.48$). Comparison of clinical and immunological manifestations showed that male patients had a higher prevalence of mucocutaneous (43.5% *vs*. 33.7%, $P = 0.005$) and a lower prevalence of musculoskeletal symptoms (44% *vs*. 54.7%, $P = 0.003$) as the initial manifestation. During the disease course, discoid rash (25.9% *vs*. 13%, $P = 0.000$) and type IV lupus nephritis (23.4% *vs*. 18.1%, $P = 0.03$) were significantly more common, whereas arthritis (61.1% *vs*. 71.7%, $P = 0.01$) and leukopenia (28.5% *vs*. 35.8%, $P = 0.024$) were significantly less common in men.

Conclusion: This study reveals gender influence on some manifestations of SLE. Considering sex differences is recommended in diagnostic and therapeutic features of the disease.

Key words: clinical manifestations, male, systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with a worldwide distribution and a wide variation in its natural history among different ethnic and geographic groups.[1] SLE is a female-predominant disease and according to different reports only 4–22% of the lupus population is male.[2] The male-to-female ratio is much higher in pre-pubertal children and after menopause.[3]

The results of previous studies have revealed that male patients develop the typical clinical manifestations of lupus as in female patients; however, certain key clinical manifestations may be different.[2] There is inconsistency about the type of differences in several studies,[2–32] which may be due to the low number of patients in most of the past surveys, variable duration

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of follow up and different pattern of disease in different ethnicities.[2]

The aim of this study was to analyze the prevalence of clinical and paraclinical features of SLE in male patients and compare them to females to investigate the impact of gender on lupus expression in a large sample of 2355 SLE patients.

METHODS

In this study medical records of 239 male and 2116 female patients with SLE were collected from the electronic database of the Rheumatology Research Center (RRC), Tehran University of Medical Sciences (TUMS), Iran. RRC is the major referral center for SLE diagnosis and management in Iran. This database includes patient information about demographic features (such as sex, age and date of disease onset), first and cumulative clinical manifestations and laboratory tests during the disease course. Laboratory tests includes complete blood count (CBC), urinanalysis, immunologic tests such as antinuclear antibody (ANA), anti-double stranded DNA (ds-DNA) and complement factors (C3 and C4). ANA and anti ds-DNA were examined via indirect immunofluorescence and nephelometry was applied in order to assess complement factors.

The protocol for the research project was approved by the Ethics Committee of the RCC. A total of 2355 SLE patients were registered from 1976 until August 2011. Enrolled patients were diagnosed by rheumatologist according to the 1997 and 1982 ACR criteria.[33,34] The follow-up visits were scheduled every 1–3 months based on disease severity. Each patient received a registry code in the database to protect their personal data.

Chi-square and Fisher's exact tests were used to compare the clinical and paraclinical manifestations of males and females at the onset and during the disease course and *t*-test was used to compare means. Potential risk/likelihood of a particular variable association with male gender was determined by odds ratio (OR). Logistic regression was used to compute ORs and 95% confidence intervals. A P-value < 0.05 was considered as statistically significant. This statistical analysis was performed by means of the SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Out of the 2355 SLE patients registered from 1976 until August 2011 in the electronic database of the RRC, 239 (10.1%) were men. The male to female ratio was 1 : 10.

Mean age at disease onset was 25 ± 11.8 (mean $\pm$ standard deviation) and 24.5 ± 10.3 years in men and women, respectively ($P = 0.48$). Mean duration of disease was 6.4 (SD = 8.3) years in men and 7.9 (SD = 10.8) years in women ($P = 0.01$).

The most common initial manifestations in men were musculoskeletal (44%) and mucocutaneous involvements (43.5%) (Table 1). During the course of disease, arthritis (61.1%) and malar rash (59%) were the most common manifestations in men. (Table 2).

Comparison of initial manifestations between the two sexes showed that male patients had significantly higher prevalence of mucocutaneous symptoms (43.5% *vs*. 33.7%, $P = 0.005$) and lower prevalence of musculoskeletal symptoms (44% *vs*. 54.7%, $P = 0.003$). The prevalence of the remaining initial manifestations was similar in both sexes (Table 1).

During the course of disease, discoid rash (25.9% *vs*. 13%, $P = 0.000$) was significantly more common in men, whereas arthritis was less commonly encountered in men (61.1% *vs*. 71.7%, $P = 0.01$).

Table 1 Comparison of clinical manifestation of SLE at disease onset in 239 male and 2116 female Iranian patients

Manifestations	Male ($N = 239$)		Female ($N = 2116$)		*P*-value	OR (95% CI)
	n	%	*n*	%		
Musculoskeletal	92	44	1026	54.7	0.003	0.65 (0.49–0.87)
Mucocutaneous	91	43.5	632	33.7	0.005	1.52 (1.14–2.03)
Hematologic	10	4.8	77	4.1	0.641	1.17 (0.60–2.31)
Neuropsychiatric	5	2.4	68	3.6	0.358	0.65 (0.26–1.63)
Renal	5	2.4	53	2.8	0.718	0.84 (0.33–2.13)
Pulmonary	3	1.4	12	0.6	0.184	2.26 (0.63–8.08)
Cardiovascular	3	1.4	8	0.4	0.090	3.40 (0.89–12.92)

SLE, systemic lupus erythematosus.

Table 2 Comparison of clinical manifestations of SLE during disease course in 239 male and 2116 female Iranian patients

Manifestations	Male (N = 239)		Female (N = 2116)		P-value	OR (95% CI)
	n	%	n	%		
Malar rash	141	59	1275	60.3	0.706	0.94 (0.72–1.25)
Discoid rash	62	25.9	276	13	0.000	2.33 (1.70–3.20)
Photosensitivity	123	51.5	1222	57.8	0.063	0.78 (0.59–1.01)
Oral ulcer	94	39.3	820	38.8	0.862	1.02 (0.78–1.35)
Arthritis	146	61.1	1517	71.7	0.01	0.62 (0.47–0.82)
Pleuritis	44	18.4	331	15.6	0.268	1.22 (0.86–1.72)
Pericarditis	24	10	188	8.9	0.554	1.14 (0.73–1.79)
Proteinuria (> 500 mg/24 h)	126	52.7	910	43	0.004	1.48 (1.13–1.93)
Cellular casts	67	28	470	22.2	0.042	1.36 (1.01–1.84)
Type 3 lupus nephritis	24	10	183	8.6	0.277	1.29 (0.82–2.04)
Type 4 lupus nephritis	56	23.4	383	18.1	0.03	1.44 (1.04–1.99)
Type 5 lupus nephritis	9	3.8	76	3.6	0.676	1.16 (0.57–2.37)
Convulsion	33	13.8	275	13	0.724	1.07 (0.73–1.58)
Psychosis	10	4.2	103	4.9	0.639	0.85 (0.44–1.66)
Hemolytic anemia	7	2.9	91	4.3	0.314	0.67 (0.31–1.47)
Leukopenia	68	28.5	758	35.8	0.024	0.71 (0.53–0.96)
Lymphopenia	84	35.1	705	33.3	0.57	1.08 (0.82–1.44)
Thrombocytopenia	46	19.2	374	17.7	0.547	1.11 (0.79–1.56)
ANA	180	75.3	1672	79	0.185	0.81 (0.59–1.11)
Anti-dsDNA	162	67.8	1509	71.3	0.254	0.85 (0.63–1.13)

SLE, systemic lupus erythematosus; ANA, antinuclear antibody; anti-dsDNA: anti-double stranded DNA.

Among men renal biopsy was performed in 151 patients and lupus nephritis was confirmed in 111 patients. Renal biopsy findings ruled out the suspected lupus nephritis in 40 patients (26.5% of suspected cases). Among women renal biopsy was undertaken in 1147 patients and in 791 cases (69.0%) lupus nephritis was confirmed. Type IV lupus nephritis was significantly more common in men (23.4% *vs*. 18.1%, $P = 0.03$) while prevalence of other types of lupus nephritis did not show any significant difference between the two sexes.

Leukopenia (28.5% *vs*. 35.8%, $P = 0.024$) was less common in men. Positive ANA and positive anti-ds-DNA were seen in 75.3% and 67.8% of men, respectively. The differences in positive ANA and positive anti ds-DNA were not statistically significant between men and women. The remaining clinical and laboratory features did not differ between men and women (Table 2).

DISCUSSION

Our study showed that lupus manifestations were different in men and women in some aspects. Over the past few decades, rheumatologists had studied male lupus to determine whether there are sex-related differences. A number of studies in SLE patients have reported inconsistent differences between men and women.[2] Based on a recent review article, this inconsistency could be due to the small sample size of SLE patients in most past surveys, variable duration of follow up and different ethnic origins.[2] The large sample size (2355 SLE patients) is an advantage of the current study in comparison with previous surveys.

Female patients constituted the majority of our studied SLE patients which was similar to other studies of large series in SLE.[3–12] The difference between mean age of disease onset in men and women was not statistically significant, as in some previous reports.[3,8,11,12] On the other hand, some studies suggested that age of SLE onset is later in men.[13–16] However, male SLE cases in our study were younger at disease onset in comparison to other studies.[3,4,8,11,12,18–20] The study by Akbarian *et al.*[1] revealed that Iranian SLE patients had younger age at disease onset in comparison to other studies.

Our study supported the finding of previous studies, as mucocutaneous symptoms were significantly more common, and musculoskeletal symptoms less common, in men at the onset and even during the course of the disease.[3,4,8,9,11,12,21] According to these results the

difference in manifestations of disease in men should be considered in SLE diagnoses.

Renal biopsy was performed in all cases of suspected lupus nephritis. During the disease course, type IV lupus nephritis was significantly more common in men in our study.Higher prevalence of renal involvement in men has been reported by several authors.[3–6,9,10,14,19,22–26] In accordance with previous studies, diffuse proliferative glomerulonephritis was the dominant histological finding in male lupus nephritis.[28–30]

Among the mucocutaneous manifestations, discoid rash was significantly higher in our men which is in accordance with the findings of past studies.[8,12,23,31] Malar rash and photosensitivity were lower in our men, the same as previous reports, although the difference was not statistically significant.[8,12,26,32]

Among musculoskeletal manifestations, arthritis was significantly less common in male SLE patients in our study. The same finding was reported by several other authors.[5,6,11–13,19,26,29]

Leukopenia was significantly less common in our men, a finding similar to other studies.[8,29] Although, hemolytic anemia and thrombocytopenia were reportedly common in other studies, this was not evident in our cohort of men.[3,5,13,23,24,27]

Table 3 shows the prevalence of organ involvement among male lupus patients in different areas around the world. Discoid rash was more common in Asian patients compared to European and American patients. The difference may be due to the role of environmental factors such as higher sun exposure as an aggravating factor. The higher incidence of renal involvement in Asian and Hispanic populations in comparison with Caucasians[33] is shown in Table 3. Although the population of Iran is composed mainly of Caucasians,[34] higher prevalence of renal involvement in our patients compared to other Caucasians[11] can be explained by the proven role of ultraviolet irradiation on aggravation of systemic features of renal involvements.[35–37] These findings may explain the important role of environmental factors in some of the clinical features of SLE.

Furthermore, a number of previous studies have underlined the role of genetics on SLE activity and disease manifestations.[38–40] Genetic predisposition may partly contribute to various manifestations of SLE among different races and across continents.

Although the number of subjects in our study was substantial, it was drawn from only one center which can be a limiting factor for this study. However our center is the major referral center for SLE diagnosis and

Table 3 The main clinical manifestations in male lupus from various studies

Country	Iran	Taiwan[19]	China[9]	Europe[11]	Mexico[3]	USA[6]
Ethnicity	Caucasian	Chinese	Chinese	Caucasian	Hispanic	Caucasian
Number of male patients	239	72	51	92	123	63
Male-to-female ratio	1 : 10	–	1 : 11.4	1 : 10	1 : 9	1 : 8.8
Mean age at disease onset (years)	25 ± 11.8	33 ± 17	31 ± 2.1	30 ± 16	27	–
Mean duration of disease (months)	76.8 ± 99.6	38 ± 36	103.6 ± 11	101 ± 96	–	10.6 ± 10
Photosensitivity	51.5	42	39	43	47.2	61.9
Oral ulcers	39.3	28	6	19	35.8	57.1
Malar rash	59	61	67	49	53.7	55.6
Discoid rash	25.5	28	18	13	11.4	19
Arthritis	61.1	53	86	74	87.8	–
Pleuritis	18.4	36	–	–	26.8	–
Pericarditis	10	29	–	–	22.8	–
Renal involvement	69	75	63	48	61	63.5
CNS Involvement	22.5	28	14	26	26.8	20.6
Hemolytic anemia	2.9	14	24	12	19.5	4.8
Leucopenia	28.5	47	16	–	38.2	38.1
Thrombocytopenia	19.2	21	25	26	20.3	23.8
ANA	75.3	97	98	97	98.3	–
Anti-dsDNA	67.8	60	67	86	79.1	–

CNS, central nervous system; ANA, antinuclear antibody; anti-dsDNA, anti-double stranded DNA.

management in Iran and our results can describe the Iranian male lupus population.

CONCLUSION

This study reveals gender influence on some clinical manifestations of SLE. Considering sex differences is recommended in diagnostic and therapeutic features of the disease.

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