ORIGINAL ARTICLE

Gender Differences in the Clinical and Serological Features of Systemic Lupus Erythematosus in Malaysian Patients

M R Azizah, MBBCh*, S S Ainol, MMed, N C T Kong, MRCP***, Y Normaznah, MD*, M N Rahim, PhD****, *Biotechnology Centre, Institute for Medical Research, Kuala Lumpur, **Hospital Penang, ***Hospital University Kebangsaan Malaysia, ****Faculty of Allied Sciences, Universiti Kebangsaan Malaysia**

Summary

An analysis of the clinical and serological features of 12 male and 122 female patients with SLE was done to determine whether sex related differences exist. We found a lower incidence of mucocutaneous symptoms and arthritis but an increased incidence of discoid lesions, pleuritis and pericarditis in males at disease onset. During the disease course, there was a lower incidence of arthritis, a similar prevalence of mucocutaneous symptoms but an increased incidence of pleuritis in males with a trend towards renal involvement. These findings were however not statistically significant except for the higher incidence of thrombosis among males. Serologically, both groups showed similar frequencies of autoantibodies and hypocomplementaemia. Although the study was small, it was shown that several sex-related differences in the clinical and serological features exist in Malaysian SLE patients.

Key Words: Autoimmunity, Immunology, Autoantibodies, Clinical, Serology, Onset

Introduction

Systemic lupus erythematosus (SLE) is a clinically heterogenous disorder of the immune system and its etiology is unknown. It is highly prevalent among young women, and known to occur rarely in men[1]. Sex hormones are suggested to modify susceptibility to and expression of SLE[2]. Oestrogen is thought to potentiate the autoimmune phenomena while androgens or male hormones are protective[2]. Several studies have compared disease manifestations between males and females and have demonstrated some clinical and immunological differences but these have not been consistent[3,4,5,6,7,8,9,10,11,12]. We have set out to answer the question of whether SLE in males differ from that in females by analysing the clinical and serological features of 12 male patients and comparing them with 122 females with SLE.

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Materials and Methods

This study consisted of 12 male and 122 female SLE patients on follow-up at the SLE Clinic of The National University Hospital of Malaysia. All satisfied the revised American College of Rheumatology criteria for SLE[13]. Information on past clinical and serological features were obtained from medical records. At the time of study, the

clinical data were recorded as part of the study protocol. Blood was obtained for serological assessment. Demographic features included age at the time of study, onset of disease, year of diagnosis and disease duration. Clinical manifestations included were fever, mucocutaneous involvement, arthritis, pleuritis and pericarditis, renal and neurological involvement, haematologic abnormalities, Raynaud's phenomenon, thrombosis and lymphadenopathy. Serological features included antinuclear antibodies (ANA) (Indirect immunofluorescence using mouse liver substrate), anti ds DNA, antibodies to extractable nuclear antigens: anti Sm, anti U1RNP, anti SSA (Ro), anti SSB (La) and anticardiolipin antibodies (IgG ACA and IgM ACA) (ELISA, IMMCO, USA), and serum complement levels (C3 and C4) (turbidimetric method).

Statistical analysis

Statistical analysis was done using conventional Chi square test and Fischer's exact test for comparing qualitative differences. The non-parametric Mann Whitney U test was used to compare age differences between groups. Data are presented as mean ± standard deviation. A p value of <0.05 was considered significant.

Results

The study group consisted of 12 (9%) males and 122 females (91%) giving a female: male ratio of 10:1. The demographic profile of patients grouped according to gender are as shown in Table I. Their mean age at study for males was 36±11 years (mean ±SD), (range, 16 - 53) compared with 34±11 years (range 14 - 69) for female patients. The mean age at onset was 30±9 years (range 13 - 43) among males while it was 26±10 years (range, 8 - 60 years) among females. However in the males, the age of disease diagnosis was 31±10 years (range 13 - 46 years) while in the females it was 27±10 years (range, 10 - 60). The mean disease duration was 7±4 years in the males and 8±5 years in the females. There was no significant age differences between the sexes with regard to age at study, disease onset, disease diagnosis and duration. Fourteen (11%) females had an earlier age of disease onset (<15 years) as compared to the males (8%). Two females but no males presented initially at age above 50 years.

Table I
Demographic Profile of 134 SLE Patients according to Sexual Distribution

	Males (N=12)	Females (N=22)
Age (yr)		
Mean	36±11	36±11
Range	16 - 53	14 - 69
Age at onset (yr)		
Mean ±SD	30±9	26±10
Range	13 - 43	8 - 60
Age at diagnosis (yr)		
Mean SD	31±10	27±10
Range	13 - 46	10 - 60
Mean disease duration	7±4	8±5
Race		
Malay	4 (33%)	52 (43%)
Chinese	6 (50%)	64 (53%)
Indian	2 (17%)	6 (5%)

Table II summarizes the frequency of the main clinical findings in patients of both sexes at the onset of the disease. Males presented less frequently with mucocutaneous symptoms (50% vs 75%) at disease onset with a lower prevalence of malar rash, photosensitivity and alopecia (42%, 33% and 42% respectively). The difference was however not statistically significant. Arthritis (17% vs 32%) was also a less frequent presentation in the males. Males had an increased incidence of discoid lesions (8% vs 4%), pleuritis (17% vs 8%) and pericarditis (8% vs 6%) as compared to the females. However, neurologic involvement and haemolytic anaemia occurred at presentation more frequently in the females (16% vs 0% and

Table II
Main Clinical Manifestations at Disease Onset

Manifestations	Male (N) (%)	Female (N) (%)	p value
Fever	6 (50)	72 (59)	ns
Mucocutaneous	6 (50)	91 (75)	ns
Malar rush	5 (42)	68 (56)	ns
Discoid lesions	1 (8)	5 (4)	ns
Photosensitivity	4 (33)	53 (43)	ns
Oral ulcers	2 (17)	19 (16)	ns
Alopecia	5 (42)	61 (50)	ns
Arthritis	2 (17)	39 (32)	ns
Pleuritis	2 (17)	10 (8)	ns
Pericarditis	1 (8)	7 (6)	ns
Renal involvement	5 (42)	55 (45)	ns
Neurologic involvement	0	19 (16)	ns
Seizures	0	4 (3)	ns
Psychosis	0	8 (7)	ns
Thrombocytopaenia	1 (8)	18 (15)	ns
Haemolytic anaemia	0	17 (14)	ns
Raynaud's phenomenon	0	7 (6)	ns
Thrombosis	0	4 (3)	ns
Lymphadenopathy	2 (17)	16 (13)	ns

Table III
Main Clinical Manifestations during Disease Course

Manifestations	Male (N) (%)	Female (N) (%)	p value
Fever	8 (67)	80 (66)	ns
Mucocutaneous	11 (91)	110 (90)	ns
Malar rush	8 (67)	85 (70)	ns
Discoid lesions	1 (8)	17 (14)	ns
Photosensitivity	7 (58)	67 (55)	ns
Oral ulcers	3 (25)	30 (25)	ns
Alopecia	8 (67)	74 (61)	ns
Arthritis	3 (25)	55 (45)	ns
Pleuritis	3 (25)	21 (17)	ns
Pericarditis	1 (8)	6 (13)	ns
Renal involvement	9 (75)	77 (63)	ns
Neurologic involvement	1 (8)	24 (20)	ns
Seizures	2 (17)	11 (9)	ns
Psychosis	1 (8)	19 (16)	ns
Thrombocytopaenia	3 (25)	27 (22)	ns
Haemolytic anaemia	1 (8)	27 (22)	ns
Raynaud's phenomenon	2 (17)	17 (4)	ns
Thrombosis	3 (25)	8 (7)*	p<0.02
Lymphadenopathy	3 (25)	24 (20)	ns

14% vs 0% respectively) but these differences were not statistically significant. At disease onset, no males presented with neurologic involvement, haemolytic anaemia, Raynaud's phenomenon and thrombosis. During the disease course (Table III), analysis of cumulative clinical manifestations showed that males and females had a similar prevalence of mucocutaneous features. Although arthritis was again lower in the males, the difference was however not significant. Males had an increased incidence of pleuritis (25 % vs 17%) and showed a trend towards renal involvement (75% vs 63%). The only statistically significant difference between the 2 groups was the occurrence of thrombosis which was found in 25% of male patients compared to 7% in the females ($p<0.02$).

Table IV summarizes the serologic findings in the two groups. Both ANA and anti ds DNA antibody frequencies were not found to differ significantly. The autoantibodies were detected in 12 (100%) of male patients and 115 (94%) of female patients. Antibodies to the extractable nuclear antigens occurred with similar frequencies in both sexes. The prevalence of anti cardiolipin antibodies and hypocomplementaemia also did not show significant differences between both groups.

Discussion

SLE is a multisystem disorder of the immune system of unknown aetiology where sex

Table IV
Cumulative Serologic Findings between Male and Female SLE Patients

Parameter	Male (N) (%)	Female (N) (%)	P value
ANA	12 (100)	115 (94)	ns
Anti ds DNA	7 (58)	82 (67)	ns
Anti SSA (Ro)	5 (42)	41 (34)	ns
Anti SSB (La)	4 (33)	60 (49)	ns
Anti U1RNP	4 (33)	44 (36)	ns
Anti Sm	2 (17)	19 (16)	ns
IgG ACA	8 (67)	77 (63)	ns
IgM ACA	1 (8)	7 (6)	ns
Low C3	1 (8)	13 (11)	ns
Low C4	2 (17)	18 (15)	ns

hormones are known to play a key role in modifying the disease; facilitating or suppressing symptoms[14,15]. It occurs widely in young women but men are rarely affected. Several reports have demonstrated that clinical and laboratory differences occur between the sexes but they are sometimes conflicting[3,4,5,6,7,8,9,10,11,12]. Females make up nearly 90% of all SLE cases, in most of the reported clinical studies, and males account for only 4 - 22%[3,7,8,11,12,16,17]. In this study, males accounted for 9% of the SLE study cohort with a female:male ratio of 10:1, a finding similar to most reports[12,13]. The mean age at onset of symptoms for our male cohort was 30±9 years though it was different in the Indian population[18]. The mean age at diagnosis was similar to that reported by others[5,19]. There was no significant differences in the age of disease onset and diagnosis between both sexes though some writers have found a delayed disease onset among males[3,5,10,17]. In contrast Ward & Studenski[17] found it to be significantly higher than in females. All the men in our study group were diagnosed before 50 years of age, a finding consistent with others[5,19].

With regards clinical manifestations, Pande *et al*[18] found an increased incidence of malar rash, photosensitivity, alopecia and mucosal ulcers demonstrating a subset of primarily mucocutaneous involvement in a major proportion of Indian males with a less severe form of the disease with a lower proportion having psychosis, lupus nephritis and hypocomplementaemia. However, in a study of 51 male patients there was a lower incidence of alopecia, thrombocytopaenia, and neurological disease but a higher incidence of pleurisy[16]. Hochberg *et al*[3] in a study of 12 males and 138 females found no significant differences in clinical and laboratory manifestations except for a high incidence of peripheral neuropathy in males. Sthoeger *et al*[20], studied 49 Israeli men and observed a higher incidence of neurological disease, nephritis, thrombocytopaenia, vasculits and hepatosplenomegaly in males. Ward & Studenski[17] found an increased prevalence of seizures among 62 men in a study involving 361 SLE patients. Kaufman *et al*[9] demonstrated an increased prevalence of renal disease and thrombocytopaenia in 52 males. Blum *et al*[4] found a predominance of renal disease and a lower prevalence of arthralgia whereas Font *et al*[8], in 30 male SLE patients, found a lower incidence of arthritis and malar rash, but higher incidence of discoid lesions and serositis at presentation. However, during follow-up, there was a lower incidence of arthritis and malar rash and a high incidence of discoid lesions and subacute cutaneous lupus erythematosus. The frequency of nephropathy, neuropathy, thrombocyotopaenia, vasculitis and serositis was similar and there were no immunological differences. Vaidya *et al*[21] in a study of 12 males from 175 patients observed a higher incidence of serositis, renal disease, Raynaud's phenomenon and anaemia in males. In another study[7] serositis was more common at onset and arthritis less common on follow-up in males. A higher incidence of renal disease and vascular thrombosis, but a lower incidence of Raynaud's phenomenon and a higher incidence of anti DNA antibodies associated with a higher prevalence of renal disease was observed by Molina *et al*[11]. Chang *et al*[6] found a lower incidence of arthritis and lymphadenopathy but a

higher incidence of renal disease. However, another study[5] found a lower incidence of musculoskeletal, cardiac and Raynauds' phenomenon but a higher incidence of hematologic manifestation. Koh *et al*[10] however in a study involving 61 Oriental males found a lower incidence of arthritis, leucopaenia and anti SSA(Ro) which did not seem to correlate with any specific clinical manifestations.

In this study, at disease onset we found a lower incidence of mucocutaneous symptoms with a lower incidence of malar rash, photosensitivity and alopecia in males though the difference was not statistically significant. There was also a lower incidence of arthritis but an increased incidence of discoid lesions, pleuritis and pericarditis. However, females were found to have an increased incidence of neurologic involvement, haemolytic anaemia, Raynaud's and thrombosis at presentation. During the course of the disease, there was a lower incidence of arthritis but a similar incidence of mucocutaneous manifestations and an increased incidence of pleuritis and showed a trend towards renal involvement. The only statistically significant difference between the 2 groups was the higher incidence of thrombosis in the male cohort. Differences of clinical expression between our studies and that of others are probably due to differences in criteria used for diagnosis of clinical manifestations or patient selection and the effects of ethnic and racial differences.

Serologically, the two groups showed similar frequencies of autoantibodies and hypocomplementaemia. This is in agreement with the findings of others[3,8,9]. However, Molina *et al*[11], found an increased incidence of anti DNA antibodies in the males, while Chang *et al*[6] found an increase in anti SSA (Ro).

Although the number of males in our study cohort was small, we have found several differences in the clinical and laboratory manifestations between male and female SLE patients, thus supporting the hypothesis that gender differences exist. Racial factors may also play a role in disease expression[3,15]. Sex-related heterogeneity in clinical and laboratory expression may possibly be due to the role of sex hormones in the pathogenesis of SLE, in modifying SLE expression and hence facilitating or suppressing disease.

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