Systemic Lupus Erythematosus in Men: A Study Among Egyptian Patients

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Abstract:
Introduction and Objectives: The aim of the study is to evaluate the influence of male gender on the pattern of SLE regarding clinical manifestations, laboratory findings, therapeutic features and outcome, and compare these findings to the female patients with SLE. Materials and Methods: Three hundred patients with SLE (260 female and 40 male) with a mean age of 29.32 years and mean disease duration 5.596 years were included in this study. A purposefully designed sheet was applied to analyze the medical records of SLE patients that were regularly following up in the rheumatology and rehabilitation department, Faculty of medicine, Cairo University. Results: The average ages of disease onset of the male and female patients were comparable. During the course of the disease, males had a significantly lower proportion of alopecia (P value 0.026), atelectasis (P value 0.036), gastritis (P value 0.046), hemolytic anaemia (P value 0.000), and a significantly higher proportion of valvular affection (P value 0.033), ischemia (P value 0.038), higher serum creatinine (P value 0.010) than female patients. Male patients presented with significantly higher ratios of malignancy than the female group (p value 0.017). Conclusion: This study has provided information regarding the features of clinical expression and morbidity in male patients, and has shown that gender is a possible factor that can influence the clinical expression of SLE.
Keywords: Epidemiology of SLE; male lupus; Systemic lupus Erythematosus

1. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, inflammatory autoimmune disorder. It may affect the skin, joints, kidneys, and other organs. Normally, the immune system controls the body's defenses against infection. In SLE and other autoimmune diseases, these defenses are turned against the body and make immune cells attack tissues ***(14)***.

Systemic Lupus Erythematosus (SLE) is often called a 'woman's disease' because of the striking differences in prevalence related to sex ***(8)***.The increased frequency of SLE among women may be attributed to differences in the metabolism of sex hormones and/or gonadotrophin releasing hormones (GnRH). Though less in men, when it does occur, SLE tends to run a more severe course, an important consideration in the diagnosis and follow up of male patients with SLE ***(19)***.

Males with Systemic Lupus Erythematosus (SLE) represent 4-22% of all SLE patients. Some distinctive features of male lupus have been observed with regard to genetic and environmental aspects of sex differences, clinical features, and outcome ***(6)***.Sex differences are still far from being generally recognized with regard to clinical manifestations and outcome in many other conditions resulting in delays in diagnosis and potentially inappropriate treatment in some patients. Thus, it seems necessary to refine diagnostic criteria and treatment guidelines for these diseases germane to either sex. In addition, sex differences affect drug action, and it has been suggested that therapy specifically tailored to men and women should be developed ***(20)***.

2. Material and Methods

We retrospectively analyzed the records of three hundred Egyptian patients with lupus who had visited the Rheumatology and Rehabilitation Department, Faculty of medicine, Cairo University. Patients with Systemic Lupus Erythematosus diagnosed according to Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus (11).

In this study, clinical manifestations, laboratory profiles, activity and damage scores were compared between male and female patients. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (2) score was used as the index of disease activity and Systemic Lupus International Collaborative Clinics /American College of Rheumatology (SLICC/ACR) Damage Index (15) was used as damage index.

A purposefully designed sheet was applied to analyze the medical records of SLE patients that were regularly following up in the department. Items included were as follow: Name, sex, age, age at onset, duration, Cumulative manifestations including: skin, eye, respiratory, cardiovascular, and renal, CNS (central nervous system), gastrointestinal, liver disease and lymph nodes enlargement. Laboratory findings: Routine investigations: CBC, urea, creatinine and urine analysis. Immunological profile: ANA, Anti-DNA, C3, C4, aCL IgG, aCL IgM, lupus anticoagulant and Anti smith. Treatment: Steroids (pulse steroids), Cyclophosphamide,

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Azathioprine, Mycophenylate myofetil, Methotrexate, antimalarial drugs and anticoagulants. Infection, Mortality (number and cause of death), SLEDAI and SLICC/ACR Damage Index were included.

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results

Analysis of the descriptive features of the studied patients showed that the age of patients ranged from 17 to 56 years old with a mean age of 29.32 ± 8.886.The age at disease onset ranged from 16 to 49 years old with a mean of 23.80 ± 7.787. The disease duration ranged from 1 to 23 years old with a mean of 5.596 ± 4.302.

The study included three hundred patients with SLE, 260 females (86.67%) and 40 males (13.33%). The age of male patients ranged from 17 to 48 years old with a mean age of 28.52 ± 8.53 years while in female patients ranged from 17 to 56 years old with a mean age of 29.47 ± 9.0 years (p value 0.528). The age at disease onset in male ranged from 16 to 43 years old with a mean age of 23.14 ± 7.595 years while in female patients ranged from 16 to 49 years old with a mean age of 23.95 ± 7.886 years (p value 0.530). The disease duration in male ranged from 1 to 14 years with a mean of 5.69 ± 4.067 years while in female patients ranged from 1 to 23 years with a mean of 5.595 ± 4.362 years (p value 0.962). No significant difference was found between male and female as regards age, age at onset and duration of the disease.

Comparing different clinical manifestations and immunological profile between studied male and female lupus patients during the course of the disease was illustrated in (Table 1) and (Table 2).

Comparison between male and female as regard nephritis the difference was not significant (P value 0.719) as regard comparing clinical and laboratory manifestations in patients had nephritis; the difference between males and females was found non-significant (Table 3).

Upon classifying SLEDAI and SLICC/ACR Damage Index, no significant difference was found between male and female (p value 0.418, 0.271 respectively) (Table 4).

Upon analyzing the most common causes of morbidity in studied patients, the difference between males and females was significant as regard cataract (P value 0.018), diabetes (P value 0.020) and malignancy (P value 0.017) (Table 5).

Upon comparing infection episodes number and its main causes between males and females in studied patients, no significant difference was found between them as regard infection episodes number but a significant difference was found between them as regard abdominal infection (P value 0.017) (Table 6).

Mortality rate was higher in males (2 patients 5%) than females (9 patients 3.5%) in our studied patient but with no statistically significant value (p- value 0.976). The causes of death in males were ESRD and malignancy while causes of death in females were variable as shown in (Table 7).

Comparison of treatment data between male and female lupus patients, no significant difference was found as regard intake frequency of I.V Cyclophosphamide (p value 1.0), Azathioprine (p value 0.34), Mycophenylate myofetil (p value 0.721), pulse steroid (p value 0.362), Antimalarials (p value 0.67), Methotrexate (p value 0.48), Anticoagulants (p value 0.826).

Table (1): frequency of clinical manifestations of patients during the course of the disease

Item	Male (n=40)		Female (n=260)		P value
	Number	Percentage	Number	Percentage	
Fever	27	67.5 %	176	67.7 %	0.981
Weight loss	1	2.5 %	26	10.0 %	0.123
Alopecia	6	15.0 %	84	32.3 %	0.026*
Malar rash	20	50.0 %	163	62.7 %	0.125
Oral ulcer	18	45.0 %	140	53.8 %	0.297
Photosensitivity	18	45.0 %	118	45.4 %	0.964
Discoid rash	2	5.0 %	13	5.0 %	1.00
Subacute skin rash	6	15 %	39	15 %	1.00
Skin vasculitis	8	20 %	56	21.5 %	0.825
Levido reticularis	2	5.0 %	9	3.5 %	0.630
Pleurisy	18	45.0 %	139	53.5 %	0.319
Pleural effusion	5	12.5 %	46	17.7 %	0.416
Atelectasis	0	0 %	26	10 %	0.036*
Pneumonitis	2	5 %	8	3.1 %	0.528
IPF	2	5.0 %	12	4.6 %	0.915
Pericarditis	10	25.0 %	54	20.8 %	0.543

Pericardial effusion	9	22.5 %	54	20.8 %	0.802
Myocraditis	0	0 %	1	0.4 %	0.694
Cardiomyopathy	3	7.5 %	20	7.7 %	0.966
Valvular affection	11	27.5 %	37	14.2 %	0.033*
Ischemia	4	10 %	8	3.1 %	0.038*
Lymph node	2	5.0 %	26	10.0 %	0.312
Arthralgia	15	37.5 %	133	51.2 %	0.108
Arthritis	28	70.0 %	179	68.8 %	0.883
Myositis	4	10.0 %	17	6.5 %	0.424
Gastritis	2	5 %	45	17.3 %	0.046*
Mesenteric vasculitis	0	0 %	2	0.8 %	0.578
Hepatomegally	18	45 %	82	31.5 %	0.093
Splenomegaly	7	17.5 %	35	13.5 %	0.493
Retinal vasculitis	1	2.5 %	10	3.8 %	0.673
Optic atrophy	0	0 %	2	0.77 %	0.578
Hemolytic anaemia	23	57.5 %	220	84.6 %	0.000*
Leucopenia	16	40.0 %	118	45.4 %	0.542
Lymphopenia	13	32.5 %	105	40.4 %	0.342
Thrombocytopenia	17	42.5 %	76	29.2 %	0.091
Nephritis	30	75%	193	74.2%	0.917
CNS affection	19	47.5%	133	51.2%	0.667
* Significant P value P value significant less than 0.05					

Table (2): Immunological results for the patients					
Item	Male (n=40)		Female (n=260)		P value
	Number	Percentage	Number	Percentage	
ANA	38	95 %	249	95.8 %	0.824
Anti DNA	36	90.0 %	216	83.1 %	0.266
C3 decrease	27	67.5 %	183	70.4 %	0.711
C4 decrease	19	47.5 %	153	58.8 %	0.177
aCL IgG	4	10.0 %	61	23.5 %	0.054
aCL IgM	3	7.5 %	58	22.3 %	0.030*
LAC	6	15.0 %	40	15.4 %	0.950
Anti smith	4	10.0 %	19	7.3 %	0.551
* Significant P value P value significant less than 0.05					

Table (3): Clinical and laboratory manifestations in patients had nephritis.					
Item	Male (n=40)		Female (n=260)		P value
	Number	Percentage	Number	Percentage	
Nephritis	30	75.0%	193	74.2%	0.917
Hematuria	24	60.0 %	181	69.6 %	0.224
Casts	23	57.5 %	119	45.8 %	0.167
Raised creatinine (>1.4)	18	45.0 %	66	25.4 %	0.010*
Increase urea	12	30 %	67	25.8 %	0.572
Renal failure	3	7.5 %	4	1.5 %	0.053
Nephrotic syndrome	2	5.0 %	8	3.1 %	0.528
Renal vein thrombosis	0	0 %	1	0.4 %	0.694
* Significant P value P value significant less than 0.05					

Table (4): SLEDAI and SLICC/ACR Damage Index in males and females in the study					
Item	Range		Mean ± SD		P value
	Male	Female	Male	Female	
SLEDAI	5 - 58	4 - 68	30.13 ± 11.359	28.70 ± 12.055	0.418
SLICC/ACR	0 – 9	0 – 8	1.83 ± 1.985	2.10 ± 1.634	0.271

Table (5): Main cause of morbidity among studied SLE patients.					
Item	Male (n=40)		Female (n=260)		P value
	Number	Percentage	Number	Percentage	
Cataract	3	7.5%	2	0.8%	0.018*
AVN	0	0 %	21	8.1%	0.089
Osteoporosis	3	7.5%	21	8.1%	1.000
Diabetes	0	0%	30	11.5%	0.020*
Malignancy	2	5.0%	0	0%	0.017*
* Significant P value P value significant less than 0.05					

Table (6): Main cause of infections in studied SLE patients.					
Item	Male (n=40)		Female (n=260)		P value
	Number	Percentage	Number	Percentage	
Infection episodes no.	13	32.5%	80	30.8%	0.812
Respiratory infection	6	15%	20	7.7%	0.134
Skin infection	4	10%	28	10.8%	1.000
Abdominal infection	2	5.0%	0	0%	0.017*
UTI	1	2.5%	26	10.0%	0.148
Otitis media	0	0%	2	0.8%	1.000
Septic arthritis	0	0%	2	0.8%	1.000
Eye infection	0	0%	2	0.8%	1.000
* Significant P value P value significant less than 0.05.					

Table (7): Causes of mortality in our studied SLE patients	
Patients	Cause of death
male pt. 1	Acute leukemia
male pt. 2	ESRD and septic shock
Female pt. 1	Thrombocytopenia and interventricular hemorrhage
Female pt. 2	Massive pulmonary embolism
Female pt. 3	Prepyloric peptic ulcer, massive hematemsis and shock
Female pt. 4	Died during valve replacement surgery
Female pt. 5	Pneumonia and active nephritis
Female pt. 6	CHF (chest infection, lung abscess and LV vegetation)
Female pt. 7	Pneumonia
Female pt. 8	Pneumonia
Female pt. 9	Sever chest infection and type 2 respiratory failure

4. Discussion

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune multisystem disease with a broad spectrum of clinical and laboratory manifestations and a variable course and prognosis (13). An old observation in Systemic Lupus Erythematosus (SLE) is the female preponderance, especially in young adults. This female-to-male ratio is much lower in prepuberal children and after menopause (5).

In the studied sample, 40 out of 300 patients (13.3%) were males with female to male ratio 6.5:1. Lopez et al. found that only 12% of patients were males, resulting in a female to male ratio of 7.5:1 (7). But, Mongkoltanatus et al study found a male lupus prevalence of 7.3%, or a female to male ratio of 17.7:1 (10). This striking gender difference indicates that male/female factors, including genetic and hormonal influences, may be important in the etiology and pathology of SLE (13).

Alopecia was more frequent in females than males and the difference was statistically significant (p value 0.026). This agrees with Garcia et al. and Mongkoltanatus et al (5, 10). Atelectasis occurred more frequent in female than male and the difference was statistically significant (p value 0.36). Tan et al found it more frequent in females without significant value (16). Valvular affection and ischemia were more frequent in male than female and the difference was statistically significant (p value 0.033, 0.038 respectively). Tan et al found a significant increase of ischemia in males and high frequent of valvular affection in females without significant value (16). As regard gastrointestinal manifestations and liver disease; Gastritis occurred more frequent in female than male and the difference was statistically significant (p value 0.046) same as Stefanidou et al (13). High frequency of CNS affection in female patients without significant difference (p value 0.667). Same results were found with Mok et al. and Mongkoltanatus et al (9, 10). Hemolytic anaemia was more frequent in females than males with statistically significant difference (p value 0.000). Same results were found by Voulgari et al (17).

Our results found high frequency of nephritis in male than female patients without significant difference (p value 0.917). Same results were found with Voulgari et al. and Garcia et al. (17, 5). Stefanidou et al found it more common in males with significant difference (13). Raised creatinine (>1.4) was found to be more common in male than female patients with statistically significant value (p value 0.010). Same results were found with Mongkoltanatus et al. (10). Another study found it more common in males but the difference was not significant (1).

aCL IgG and aCL IgM were frequently positive in females than males and this difference was statistically significant as regard aCL IgM (p value 0.054, 0.030 respectively). Same results with Renau and Isenberg, (12). Tan et al found that anticardiolipin were frequently positive in males without significant difference (16). Garcia et al found that aCL IgG was significantly positive in males, while aCL IgM was frequently positive in females without significant difference (5).

Considering the relation between gender and disease activity score (SLEDAI), no significant difference was found (p value 0.418). Carvalho et al and Wang et al were found same results among lupus patients with nephritis (3, 18). Ding et al study on hospitalized patients showed that the SLEDAI score was significantly higher in male patients than in

female patients (means, 16.8 vs. 12.8, P=0.038) (4). Considering the relation between gender and (SLICC/ACR) Damage Index, no significant difference was found (p value 0.271) Garcia et al and Voulgari et al found same results (5, 17).

As regard incidence of morbidity among our SLE patients, it was found that cataract was more frequent in males than females and the difference was statistically significant (p value 0.018). Stefanidou et al found cataract more frequent in males but the difference was not significant (13). On the other hand, Tan et al found it more frequent in females with no significant value (16).Diabetes was more frequent in females and the difference was significant (p value 0.020). Stefanidou et al and Tan et al found it more frequent in males but without significant value (13, 16). Malignancy was more frequent in males than females and the difference was statistically significant (p value 0.017). Stefanidou et al and Tan et al found it more frequent in males but without significant value (13, 16).

Males were more frequently had infections than females (32.5% vs. 30.8%) and the difference was not significant (p value 0.812). Males were frequently presented with abdominal and respiratory infections and the difference was significant as regard abdominal infections (p value 0.017, 0.134 respectively). While skin infections, UTI, otitis media, septic arthritis and eye infection were more frequent in females and the difference was not significant (p value 1.0, 0.148, 1.0, 1.0, 1.0 respectively). Aranow et al and Garcia et al study found that infections were more common in males and the difference was not significant (1, 5). Stefanidou et al study found that respiratory, skin and abdominal infections were more frequent in males than females and the difference was significant as regard respiratory and skin infections (13).

A higher mortality rate was found among male patients (5% vs. 3.5%) but with no statistically significant value (p value 0.976). Same results were found with Carvalho et al., (3). Tan et al study found significant increase of mortality among male patients (16). Renau and Isenberg found high frequency of mortality in females than males and the difference was not significant (12).

High frequent intake of Cyclophosphamide (CYC) and daily oral steroids either < 15 mg or > 40 mg were found in male patients (p value 1.0, 0.66, 0.18 respectively). High frequent intake of Azathioprine (AZA) (p value 0.0.34), Mycophenylate myofetil (MMF) (p value 0.721), Pulse steroid (p value 0.362), anticoagulants (p value 0.825), daily oral steroids (15-35mg) (p value 0.14), antimalarial drugs (p value 0.67) and methotrexate (MTX) (p value 0.48) were found among female patients, with no statistically significant value. Wang et al study showed high frequent intake of CYC and MMF in females and AZA and LEF in males and the difference was not significant (18). Aranow et al found high intake of steroids > 30 mg, CYC and hydroxychloroquine in females and high intake of AZA in males without significant difference (1).

5. Conclusions

We found that there were some differences in clinical and laboratory manifestations between Egyptian male and female lupus patients. Thrombocytopenia, renal failure, infections, malignancy and mortality were more commonly observed in male lupus patients; whereas alopecia, anemia and CNS affection were more common in females. Our findings were similar to previously reports from several studies. The low incidence and prevalence of SLE in male patients has led to many paradoxical findings. More studies will be needed to solve this issue.

Abbreviations

SLICC : Systemic Lupus Erythematosus Disease Activity Index.
SLICC/ACR: Systemic Lupus International Collaborative Clinics/ American College of Rheumatology.
CBC : Complete blood picture.
ANA : Antinuclear antibody.
Anti-DNA : Anti-Double stranded DNA.
C3 : Complement 3.
C4 : Complement 4.
aCL IgG : Anti Cardiolipin Immunoglobulin G antibody.
aCL IgM : Anti Cardiolipin Immunoglobulin M antibody.
LAC : Lupus Anti-Coagulant.
ESRD : End stage renal disease.
UTI : Urinary tract infection.
AVN : Avascular necrosis.

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