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ORIGINAL ARTICLE

Systemic lupus erythematosus in Iran: a study of 2280 patients over 33 years

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Abstract

Objective: Systemic lupus erythematosus (SLE) as a chronic autoimmune disease has a worldwide distribution. There is a wide variation in the natural history of SLE among different ethnic and geographic groups. The aim of this study was to show the manifestations of SLE in Iranian patients.

Methods: The study was on manifestations of SLE according to the database of the Rheumatology Research Center (RRC), Tehran, Iran, on registered patients during the period of 1976 to 2009.

Results: A total of 2280 SLE patients (2052 female and 228 male) were studied. The female : male ratio was 9 : 1 and the mean age at presentation was 24.4 ± 10.4 years. Prevalence of manifestations included: musculoskeletal (83.2%), cutaneous (81.1%), renal (65.4%), neuropsychiatric (23.4%), pulmonary (21.5%), cardiac (17.2%), and hematologic (66.4%) symptoms. There was positive antinuclear antibodies in 86.4% and anti-DNA in 82.3% of patients. Overlap syndrome and positive family history with other autoimmune diseases were detected in 7.6% and 3.4% of patients, respectively.

Conclusion: In our patients the prevalence of cutaneous involvement was similar to those of nearby countries (with similar climate). Renal involvement was seen more than some other countries especially more than European countries, while other manifestations (such as hematologic and joint involvement) were similar to European countries (with similar ethnicity). We may conclude that genetic and/or climatic factors may lead to different presentations of lupus.

Key words: epidemiology, clinical aspects, Iran, systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease with diverse clinical manifestations in association with auto-antibodies to components of the cell nucleus. SLE as a chronic autoimmune disease has a worldwide distribution. There is a wide variation in the natural history of SLE among different ethnic and geographic groups.[1] SLE in Iran as an Asian country is relatively common with prevalence of 40 per 100 000.[2] As our SLE registry is one of the largest series in the Asia–Pacific region, the data on different aspects of the disease in Iranian patients may be of interest. In this article, we explore the manifestations of SLE in Iranian patients.

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MATERIALS AND METHODS

This study is on manifestations of SLE according to the database of the Rheumatology Research Center (RRC), Tehran University of Medical Sciences, Tehran,

Iran, as a major referral center for rheumatic diseases in Iran. The study examined registered patients during the period 1976 to 2009. All lupus patients fulfilling the American College of Rheumatology (ACR) criteria for classification of SLE[3,4] were included. Registered data included demographic features (such as sex, age at onset, age at diagnosis and date of the first visit), and different manifestations of the patients. Laboratory tests included complete blood count (CBC) and platelet count, erythrocyte sedimentation rate (ESR) in the first hour, C-reactive protein (CRP), serum creatinine, urinalysis, immunologic tests such as antinuclear antibody (ANA), anti-double stranded DNA (ds-DNA), complement factors (C3 and C4; complement hemolytic activity 50% [CH_{50}]) and rheumatoid factor (RF). Indirect immunofluorescence method was used to detect ANA and anti ds-DNA antibodies. Complements were assessed by nephelometry. Renal biopsy specimens were studied by light and immunofluorescence microscopy. Classification of lupus nephritis was based on WHO classification criteria 1982.[5] Patients' follow-up visits were every 1–3 months depending on the severity of the disease.

Special software was developed specifically to register patient data. This software has 266 items that were checked for each patient. The database was updated after each patient follow-up visit. All statistical calculations were performed by the software. Descriptive data are presented as percentage ± 95% confidence interval (95% CI), means ± standard deviation (SD), and medians. Chi-square test was used to compare the two groups. Odds ratio and 95% CI were used to present the strength of association (P-value < 0.05). The study was approved by the local ethical committee.

RESULTS

Demographic characteristics

A total of 2280 SLE patients were studied. There were 2052 females and 228 males, with a female : male ratio of 9 : 1. The mean age at presentation was 24.4 ± 10.4 years. The mean disease duration was 7.1 ± 10.3 years, and the mean follow-up time was 5 ± 9.6 years. A positive family history of SLE and other autoimmune diseases was found in 3.4% (95% CI: 2.7–4.1) of patients.

Constitutional manifestations

Constitutional manifestations were present in 61.9% of patients. They were fever in 46.9%, fatigue and malaise in 35.7%, weight loss in 31.7%, anorexia in 27.8% and chills in 17.5% of patients (Table 1).

Musculoskeletal involvement

Musculoskeletal involvement was the most common manifestation (83.2%). Arthritis was seen in 51.9%, arthralgia without arthritis in 31.3%, joint deformity in 4.2%, articular erosion in 0.9%, avascular necrosis (AVN) in 4.6%, muscle weakness in 15.9%, myalgia in 10.2%, and myositis in 2.9% of patients (Table 1).

Mucocutaneous involvement

Mucocutaneous manifestations were present in 81.1% of patients. Malar rash developed in 60% of patients, photosensitivity in 56.4%, oral ulcer in 38.5%, and discoid lesions in 14.6% (Table 1).

Renal involvement

Renal involvement was present in 65.4% of patients. Proteinuria was detected in 54.6%, hematuria (≥ 5 red blood cells/high power field) in 41.8% and renal casts (cellular or granular) in 23.5% of patients. Lupus nephritis Class I was seen in 0.1% of patients, Class II in 3.8%, Class III in 8.6%, Class IV in 18.5%, Class V in 3.5%. Diffuse proliferative lupus nephritis (Class IV) was the most common type of lupus nephritis in our patients. Increased creatinine (more than 1.5 mg/dL) was detected in 24.5% (95% CI: 22.7–26.3) of patients with renal involvement (Table 1).

Neuropsychiatric involvement

Neuropsychiatric involvement was present in 23.4% of patients. Seizure was seen in 13.0%, psychosis in 4.9%, and peripheral neuropathy in 5.7% of patients (Table 1).

Pulmonary involvement

Pulmonary involvement was seen in 21.5% of patients, pleuritis in 16%, lupus pneumonitis in 2.0%, interstitial fibrosis in 0.9%, pulmonary embolism in 0.8%, and pulmonary hypertension in 0.2% (Table 1).

Cardiovascular involvement

Cardiovascular involvement was present in 17.2% of patients. Pericarditis was seen in 9.2%, valvular lesion in 3.8%, and myocarditis in 2.8% of patients.

Raynaud's phenomenon was seen in 15.2%, livedo reticularis in 3.2%, and thrombophlebitis in 3.6% of patients (Table 1).

Table 1 Manifestations in 2280 patients with systemic lupus erythematosus

	Number	Percentage	95% CI
Constitutional manifestations	1411	61.9	59.9–63.9
Fever	1069	46.9	44.9–48.9
Fatigue	815	35.7	33.5–37.5
Weight loss	722	31.7	29.8–33.6
Anorexia	634	27.8	26–29.6
Chills	399	17.5	15.9–19.1
Musculoskeletal manifestations	1896	83.2	81.7–84.7
Transient arthritis	1184	51.9	49.8–54
Arthralgia without arthritis	713	31.3	29.3–33.3
Articular erosion	21	0.9	0.5–1.3
Avascular necrosis (AVN)	105	4.6	3.7–5.5
Myositis	65	2.9	2.2–3.6
Mucocutaneous manifestations	1848	81.1	79.5–82.7
Malar rash	1367	60	58–62
Photosensitivity	1287	56.4	54.4–58.4
Hair loss	1172	51.4	49.3–35.5
Oral ulcer	887	38.5	36.5–38.5
Discoid lesion	332	14.6	13.2–16
Renal manifestations	1492	65.4	63.4–67.4
Proteinuria	1245	54.6	52.6–56.6
Hematuria	952	41.8	39.8–43.8
Cellular cast	536	23.5	21.8–25.2
Renal biopsy	804	35.3	33.3–37.3
Type I	3	0.1	0.0–0.2
Type II	86	3.8	3.0–4.6
Type III	196	8.6	7.4–9.8
Type IV	422	18.5	16.9–20.1
Type V	80	3.5	2.7–4.3
Neuropsychiatric involvements	534	23.4	21.7–25.1
Convulsion	297	13.0	11.6–14.4
Psychosis	112	4.9	4.0–5.8
Peripheral neuropathy	131	5.7	4.7–6.7
Pulmonary manifestation	491	21.5	19.8–23.2
Pleuritis/pleuresia	364	16	14.5–17.5
Lupus pneumonitis	45	2.0	1.4–2.6
Pulmonary hypertention	4	0.2	0.0–0.4
Cardiac manifestations	392	17.2	15.7–18.7
Pericarditis	209	9.2	8.0–10.4
Valvular lesions	87	3.8	3.0–4.6
Myocarditis	63	2.8	2.1–3.5
Hematologic manifestations	1514	66.4	64.5–68.3
Leucopenia	801	35.1	33.1–37.1
Hemolytic anemia	93	4.1	4.9–3.3
Thrombocytopenia	401	17.6	16–19.2
Immunologic manifestations	–	–	–
ANA	1967	86.4	84.7–88.1
Anti-dsDNA	1887	82.3	80.4–84.2
Low C3	1115	48.9	46.8–51
Low C4	1143	50.1	48–52.2

ANA, anti-nuclear antibody; Abti-dsDNA, anti-double stranded DNA; C3/C4, complement factors; 95% CI, 95% confidence interval.

Reticulo-endothelial system

Lymphadenopathy was detected in 13.7% (95% CI: 12.3–15.1) and splenomegaly in 12.1% (95% CI: 10.8–13.4) of patients.

Overlap syndrome

Association of SLE with other autoimmune diseases was presented in 7.6% (95% CI: 6.5–8.7) of patients. Polymyositis/dermatomyositis was seen in 4.1%, scleroderma in 2.5%, and rheumatoid arthritis in 1.8% of patients.

Laboratory features

Leukopenia (white blood cells ≤ 4000/μL) was present in 35.1%, thrombocytopenia (platelets ≤ 100 000/μL) in 17.6%, and hemolytic anemia in 4.1% of patients.

Positive ANA was seen in 86.4%, high anti-dsDNA in 82.3%, low C3 in 48.9%, low C4 in 50.1%, and low CH_{50} in 17.8% of cases. ESR ≥ 100 mm/h was detected in 25.4%, positive CRP in 42.1% and positive RF in 20.4% of patients (Table 1).

Comparison (present study and previous cohorts)

The comparison between our study (Iran) and previous cohorts (Saudi Arabia,[6] Lebanon,[7] Kuwait[8] and Europe[9,10]) is reported in Table 2.

DISCUSSION

There are various reports from different parts of the world on the prevalence and characteristics of SLE. Whether the variations can be attributed to genetic or environmental factors has been the subject of a series of debates. In this study, we reported manifestations of 2280 Iranian patients with SLE. Iran, as a country in the Middle East, due to the ethnicity of its people (i.e., similar to European countries), is a good candidate for evaluation of the effects of genetic or environmental factors on different features of the disease. The population of Iran is composed mainly of Caucasians (71.4%).[2]

In Table 2 we compare the characteristics in our patients with those reported from countries in the same region (Middle East) mainly with Arab ethnicity (Saudi Arabia,[6] Lebanon[7] and Kuwait[8]), and large series from Europe[9,10] with the same ethnicity as Iran (mainly Caucasians).

The higher prevalence of disease in females is similar in all reports, but the lowest ratio was reported in

Table 2 Comparison of SLE manifestations between present and previous cohorts

Authors	Present study	Alballa SR *et al.*[6]	Ulthman I *et al.*[7]	Al-Jarallah K *et al.*[8]	Cervera R *et al.*[9,10]
Geographic area	Middle East	Middle East	Middle East	Middle East	Europe
Population	Iranian	Saudi	Lebanese	Kuwait	European
Number of patients	2280	87	100	108	1000
Female to male ratio	9/1	9/1	6.1/1	10/1	9.8/1
Median age of onset	21.7	25.3 ± 10.5 (mean)	25	31.5	29
Photosensitivity	56.4%	26% (P = 0.0000) OR = 3.6 (CI = 2.22–5.83)	16% (P = 0.0000) OR = 6.8 (CI = 3.95–11.66)	48% (P = N.S)	22.9% (P = 0.0000) OR = 4.3 (CI = 3.67–5.15)
Malar rash	60%	56% (P = N.S)	52% (P = N.S)	43% (P = 0.0003) OR = 2.04 (CI = 1.38–3.03)	31.3% (P = 0.0000) OR = 3.3 (CI = 2.85–3.9)
Discoid lesion	14.6%	18% (P = N.S)	19% (P = N.S)	10% (P = N.S)	7.8% (P = 0.0000) OR = 2.02 (CI = 1.56–2.62)
Oral ulcer	38.5%	16% (P = 0.0000) OR = 3.3 (CI = 1.83–5.81)	40% (P = N.S)	33% (P = N.S)	12.5% (P = 0.0000) OR = 4.3 (CI = 3.56–5.37)
Arthritis	51.9%	91% (P = 0.0000) OR = 0.1 (CI = 0.05–0.23)	95% (P = 0.0000) OR = 0.06 (CI = 2.23–0.14)	87% (P = 0.0000) OR = 0.02 (CI = 0.091–0.284)	48.1% (P = 0.043) OR = 1.2 (CI = 1.004–1.35)
Serositis	21.8%	56% (P = 0.0000) OR = 0.2 (CI = 0.14–0.33)	40% (P = 0.0000) OR = 0.4 (CI = 0.28–0.63)	29% (P = N.S)	NR
Renal	65.4%	63% (P = N.S)	50% (P = 0.0015) OR = 1.9 (CI = 1.27–2.8)	37% (P = 0.0000) OR = 3.2 (CI = 2.16–4.8)	27.9% (P = 0.0000) OR = 4.9 (CI = 4.16–5.76)
Neuropsychiatric	23.4%	26% (P = N.S)	19% (P = N.S)	23% (P = N.S)	19.4% (P = 0.0000) OR = 1.3 (CI = 1.06–1.53)
Hematologic	66.4%	NR	47% (P = 0.0001) OR = 2.2 (CI = 1.49–3.33)	53% (P = 0.0035) OR = 1.8 (CI = 1.2–2.6)	NR
Leukopenia	35.1%	NR	17% (P = 0.0001) OR = 2.7 (CI = 1.58–4.54)	83% (P = 0.0000) OR = 0.1 (CI = 0.07–0.18)	NR
Hemolytic anemia	4.1%	NR	10% (P = 0.0043) OR = 0.4 (CI = 0.19–0.76)	NR	4.8% (P = N.S)

Table 2 (continued)

Authors	Present study	Alballa SR *et al.*[6]	Ulthman I *et al.*[7]	Al-Jarallah K *et al.*[8]	Cervera R *et al.*[9,10]
Thrombocytopenia	17.6%	NR	33% (P = 0.0001) OR = 0.4 (CI = 0.28–0.66)	26% (P = 0.027) OR = 0.6 (CI = 0.39–0.95)	13.4% (P = 0.0028) OR = 1.4 (CI = 1.12–1.7)
ANA	86.4%	98% (P = 0.0012) OR = 0.15 (CI = 0.04–0.61)	87% (P = N.S)	94% (P = 0.01) OR = 0.4 (CI = 0.16–0.86)	96% (P = 0.0000) OR = 0.3 (CI = 0.19–0.37)
Anti-dsDNA	82.3%	93% (P = 0.0057) OR = 0.3 (CI = 0.15–0.79)	50% (P = 0.0000) OR = 4.6 (CI = 3.09–6.97)	58% (P = 0.0000) OR = 3.3 (CI = 2.23–4.93)	78% (P = 0.004) OR = 1.3 (CI = 1.09–1.57)

ANA, anti-nuclear antibody; Anti-dsDNA, anti double stranded DNA; NR, not reported; N.S, not significant; *P*, *P*-value; OR, odds ratio; NR, not reported; N.S, not significant.

Lebanon (6.1/1)[7] and highest in Kuwait (10/1).[8] Our patients showed younger age at disease onset in comparison to other studies. We have no explanation for this; however genetic and/or environmental factors may be responsible.

The prevalence of cutaneous manifestations (notably malar rash and discoid lesions) in our patients were similar to nearby countries[6–8] but approximately twice more common than in European patients.[9,10] Renal involvement was similar to Saudi Arabia[6] but more than other countries in our region.[7,8] Although it was higher than regional countries, the greatest difference was seen in European countries (renal involvement was five times more than in European countries).[9,10] Iran is located in a lower latitudinal position with more intense ultraviolet irradiation.[11] This result can be explained by the proven role of ultraviolet on aggravation of cutaneous manifestations.[12] It is stated that sunlight not only aggravates cutaneous lesions but also potentiates systemic features of disease such as renal involvement.[13] Other environmental factors such as temperate climate, nutritional and socioeconomic factors in developed and developing countries significantly influence the frequency of renal involvement.[14]

The prevalence of joint involvement and hematologic abnormalities (notably hemolytic anemia and thrombocytopenia) in our patients were the same as European patients[9,10] and much lower than those reported in series from neighboring countries.[6–8] This may be related to the more important role of genetic factors on these characteristics.

Neuropsychiatric involvement in our study was similar to other studies.[6–10]

Positive ANA in our study was lower than previous cohorts[6,8–10] but anti-dsDNA was higher than some countries of our region[7,8] and similar to European countries,[9,10] which we could not explain.

Seventy-eight (3.4%) of our SLE patients had relatives with an autoimmune disease (SLE, RA and/or other autoimmune diseases). In comparison with European countries the positive family history in our study was lower than reports from Cooper *et al.*[15] (6%) and Alarcon-Segovia *et al.*[16] (14.1%). There has been no report on the prevalence of positive family history from nearby countries. Regarding similar ethnicity of Iranians and Europeans, this difference can indicate a role of both genetic and environmental factors in the probability of family history with SLE and/or any autoimmune disease.[16]

CONCLUSION

In our patients the prevalence of cutaneous involvement (such as malar rash and discoid lesions) was similar to those of nearby countries (with similar climate). Renal involvement was seen more than some other countries, especially more than European countries, while other manifestations (such as hematologic and joint involvement) were similar to European countries (with similar ethnicity). We may conclude that genetic and/or climatic factors may lead to different presentations of lupus.

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