Original Article

Ethnic distribution and clinical features of systemic lupus erythematosus in the Sudan

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التوزيع العرقي والمظاهر السريرية للذئبة الحمامية الجهازية في السودان

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خلفية:
الذئبة الحمامية الجهازية (SLE) هو التهاب مزمن ذو مناعه ذاتيه يصيب عدة أجهزة بالجسم ويتميز بفترات الهجوع والانتكاسات. ومن المعتقد ان هنك تطوير جيني لدى الأشخاص المعرضين لواحد أو أكثر من المحفزات البيئية. خاصية سكان السودان المختلطة عرقيا يتيح فرصة للنظر في أثر العرق على توزيع منهجي والتعبير عن هذا المرض.
المرضى وطرائق البحث:
هذه الدراسة شملت عدد ٨٧ مريضا توجد بهم المعايير السريرية والمختبرية لتشخيص التهاب الذئبة الحمامية الجهازية (SLE) بثلاثة مراكزطبية مرجعيه بالخرطوم. تم جمع معلومات من المرضى تشتمل على تاريخ مرضي وكشف سريري مع إجراء الفحوصات اللازمة وقد أخذت عينات للكلى للمرضى المصا بين بألتهاب الكلى الذئبى..
النتائج:-
ثلاثة وثمانون من ٨٧ مريضا (٩٥,٤ ٪) من الإناث (نسبة الإناث إلى الذكور ١:٢٠,٦). متوسط العمر عند التشخيص ٣١,٨٩ سنة (مجموعة ٢١-٣٠).
هذا المرض موجود بنسبة أكبر فى السلالات المختلطة عرقيا (عرب من أصل أفريقي) حيث تشكل ٩٤,٣ ٪ وبنسبة أقل فى نقية السلالات الأفريقية. تشكل سلالة النوبة ٥,٧ ٪ وهى سلالة قديمة من القبائل التي تعيش في وسط وشمال السودان. ليس هنالك مرضى من القبائل الزنجية من جنوب وغرب السودان. . تلاحظ إصابة أجهزة متعدده فى الجسم بالمرض كما هو شائع فى أماكن أخرى كما أن معظم المرضى (٩٦,٦%) توجد لديهم أضداد النوى (ANA) بينما يوجد (anti-dsDNA) فى (٥١,١%) مريضا.
الخلاصة:-
مرض الذئبة الحمامية الجهازية فى المرضى السودانيين يشابه الحالات الموجودة فى المناطق الأخرى وقد لوحظ وجود أكثر للمرض فى السلالات المختلطة عرقيا وأقل فى السلالات الخالصة من أصل أفريقى. وهذه الدراسة تدعم ملاحظة أن التهاب الذئبة الحمامية الجهازيه نادر في الأفارقة السود الذين يعيشون في افريقيا ، ومع ذلك فإنه ليس من غير المألوف فى السلالات العربية الأفريقية المختلطة.

Abstract

Background

Systemic lupus erythematosus (SLE) is a multisystem chronic inflammatory autoimmune disease characterized by periods of remissions and relapses. It is thought to develop when genetically predisposed individuals are exposed to one or more environmental triggers. The ethnically mixed population of the Sudan offers an opportunity to look into the effect of ethnicity on the distribution and systemic expression of the disease.

Patients and methods

Eighty seven consecutive patients fulfilling the clinical and laboratory criteria for the diagnosis of SLE were prospectively interviewed and examined using a unified protocol in three medical clinics in different parts of Khartoum. Appropriate investigations, including renal biopsies were carried out when indicated.

Results

Eighty three of the 87 patients (95.4%) were females (female to male ratio 20.6:1). Mean age at diagnosis was 31.89 years (range 21-30). The disease was most frequently seen in tribes of mixed ethnicity (Afro-Arabs) and least common in pure African tribes. Thus, subjects with Afro-Arab ancestry constituted 94.3% of the sample seen whereas, subjects from Nubian ancestry (descendents from ancient tribes living in central and northern Sudan) were 5.7% of the group and no subjects from the black tribes of Southern and Western Sudan were represented.

Conclusion

The disease affected multiple systems as seen elsewhere. Most of the patients (96.6%) were antinuclear antibodies (ANA) positive while (51.1%) were antidouble stranded dioxyribonucleic acid (Anti-dsDNA) positive.

The clinical features of SLE in our patients are comparable to what has been studied in the region. However, there was an overwhelming tendency of the disease to affect subjects of mixed ethnicity and less affection of subjects of pure African ancestry. The study is in support of the observation that SLE is rare in Black Africans living in Africa, however, it is not uncommon in subjects with Afro-Arab genetic admixture.

Key words: SLE, Africa, Sudan, Lupus nephritis.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune multisystem disease in which organs, tissues, and cells undergo damage mediated by tissue-binding auto antibodies and immune complexes[1]. It is protean in its manifestations and follows a relapsing and remitting course[1,2].

Although the specific cause of SLE is not known, multiple factors are associated with the development of the disease. These include: genetic, racial, hormonal and environmental factors. In patients who are predisposed genetically, exposure to natural ultraviolet radiation viruses and drugs have been implicated in precipitating or exacerbating SLE[3,4].

The epidemiology of SLE in people of African origin varies from one geographical setting to another. It appears to be rare in West Africa, increasing in frequency in Central and Southern Africa. However, SLE seems to frequently affect Africans living in America, the Caribbean islands and Europe. Whether this is predominantly genetic or

environmental may be difficult to unravel. Most African-Americans and Caribbean's came from West Africa, where SLE is now rare[5]. Despite improvements in overall survival rates, patients with SLE still have a death rate that is three times that of the general population and an increase up to 4.0 and 4.92 folds has been reported in some studies[3].

The diagnosis of SLE is based on characteristic clinical features and autoantibodies. Criteria for classification of the disease were made by the American College of Rheumatology (ACR) and revised in 1982. Any combination of 4 or more of 11 criteria, well-documented at any time during a patient's history, makes it likely that the patient has SLE (specificity and sensitivity are ~95% and 75% respectively)[5]. In many patients, additional criteria accrue overtime. Antinuclear antibodies (ANA) are positive in >95% of patients during the course of the disease; repeated negative tests suggest that the diagnosis is not SLE. High titer IgG antibodies to double-stranded DNA and antibodies to the Sm antigen are both specific for SLE and therefore, favor the diagnosis in the presence of compatible clinical manifestations. The presence in an individual of multiple autoantibodies without clinical symptoms should not be considered diagnostic for SLE although, such persons are at increased risk[5].

Patients and methods

Study design

This is a prospective and descriptive cross-sectional hospital based study done in the Nephrology Units of three major hospitals in Greater Khartoum: Omdurman Military Hospital, Omdurman Teaching Hospital and the National Ribat University Hospital, in the periods between January 2005 and August 2007. The three hospitals serve different populations in Greater Khartoum, the capital of the Sudan.

Inclusion criteria were: the patients should be of Sudanese nationality, fulfilling the 1982 revised criteria for diagnosis of SLE according to American College of Rheumatology (ACR) and consenting to participate in the study.

Data were collected through history, physical examination and the required Laboratory investigations which were performed according to the standard hospital procedures. Renal biopsies were performed when indicated. Biopsy specimens were studied under light microscopy and immunofluorescence (IF). Renal biopsies were studied, diagnosed and classified according to the World Health Organization classification of Lupus nephritis.

Data were entered in the computer and software Statistical Package for Social Science program (SPSS) for Windows was used for the analysis. Chi square test was used to compare percentages. P-value <0.05 was considered significant.

Results

A total of 87 patients with SLE were enrolled in the study. Eighty three (95.4%) were females. The females to males ratio was 20.6:1. The mean age at diagnosis was 31.89 years (± 11.62 SD) and the range was 21-30 years. All patients were Sudanese, 82 (94.3%) were Arabs with Nubian (Kushite) roots and five patients (5.7%) were non-Arab Black Africans (Nuba tribe). No patient was identified from African tribes of Southern and Western Sudan, though many of the inhabitants of Central Khartoum are from these tribes. Constitutional symptoms of fever and fatigue were found in 58 (66.7%) and 68(78.2%) patients respectively. Fifty-one patients (58.6%) had history of recurrent illness while 36 (41.4%) presented with acute illness. History of repeated abortions was found in 9 of the 83

female patients (10.8%). Four patients (4.6%) patients had history of DVT but none of them fulfilled the antiphospholipid syndrome (APS) criteria. Family history of the same illness found in 11(12.6%) of cases. Tables 1 to 4 summarize the clinical features of SLE in the study group. Fig. 1 shows results of renal biopsy and Table 5 shows ethnic variation.

Table 1: Clinical manifestations and serological testing of SLE in the target population (n=87).

Criteria	No. of Patients	Percent
Malar rash	64	73.6%
Photosensitivity	28	32.2%
Oral ulcer	47	54%
Discoid lupus	2	2.3%
Arthritis/Arthralgia	83	95.4%
Hematological	33	37.9%
Neuropsychiatric	12	13.9%
Renal involvement	55	63.2%
Serositis	33	37.9%
Positive ANA	84	96.6%
Positive anti-dsDNA	45	51.1%

Table 2: Hematological manifestation among patients (n=87).

Hematological disorders	No. of patients	Percent
Autoimmune hemolytic anemia (Hb <12 g/dL)	12	13.8%
Leucopenia (<4000/µL)	19	21.8%
Thrombocytopenia (<100,000/µL)	6	6.9%
Normal ESR	5	5.7%
ESR> 30 in 1hour	48	55.2%
Three figures ESR	34	39.1%

Table 3: Renal involvement among patients (n=87).

Presentation	No. of patients	Percent
Oligurea	17	19.5%
Lower limbs oedema/Periorbital oedema	35	40.2%
Systemic hypertension	15	17.2%
Hematuria (> 3 RBCs)	34	39.1%
Active urine sediment	34	39.1%
Nephrotic syndrome (24 hrs urine protein > 3 grams)	26	29.9%
S.creatinine > 1.4 mg/dl	17	19.5%

Table (4) Comparison of clinical features in SLE patients with positive serological tests (n=87).

Presentation	ANA		Anti-dsDNA	
	+ve	P value	+ve	P value
Skin rash (64)	61	0.393	31	0.218
Photosensivity (28)	27	0.693	15	0.497
Discoid rash (2)	1	0.068	2	0.265
Oral ulcer (47)	44	0.153	19	0.019
Arthritis (83)	80	0.867	42	0.335
Hematological disorders (33)	32	0.680	15	0.244
Serositis (33)	33	0.234	19	0.264
CNS involvement (12)	12	0.637	7	0.429
Renal disorders (55)	53	0.696	35	0.003

(P-value <0.05)

Figure 1 shows the distribution of the classes of lupus nephritis in the 50 patients who had renal biopsies performed.

Fig. 1: Renal biopsy in patients with lupus nephritis (n=55).

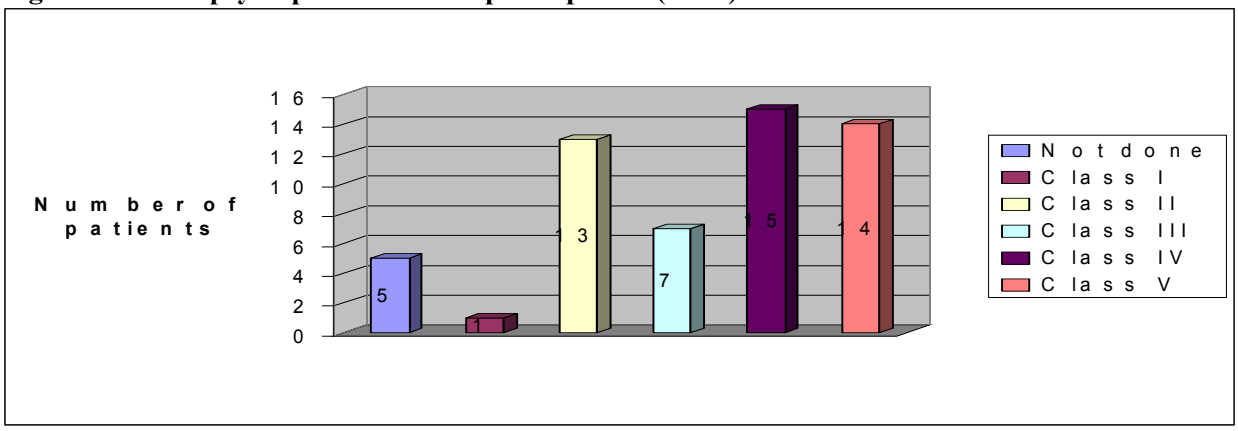

Table 5 compares the clinical features among the two major ethnic groups of the Sudan.

Table 5: Clinical and laboratory manifestations among the tribes in patients with SLE (n=87)

ACR criteria	Afro-Arabs (n=82)%	Non-Arab Blacks (n=5)%	P value
Skin rash	62 (75.6)	2 (40)	0.113
Photosensivity	27 (32.9)	1 (20)	0.480
Discoid rash	2 (2.4)	0 (0)	0.888
Oral ulcer	46 (56.1)	1 (20)	0.134
Arthritis	78 (95.1)	5 (100)	0.786
Hematological disorders	32 (39)	1 (20)	0.368
Serositis	28 (34.1)	5 (100)	0.006
CNS involvement	11 (13.4)	1 (20)	0.533
Renal disorders	50 (61)	5 (100)	0.094
ANA	79 (96.3)	5 (100)	0.836
Anti-dsDNA	42 (51.2)	3 (60)	0.532

(P-value <0.05)

Discussion

To the best of our knowledge no epidemiological studies on SLE have been carried out before in the Sudan. However, we have previously reported that the prevalence of lupus nephritis in the Sudan was 14.7% of all glomerulonephritidis[6].

Worldwide, different races appear to have varying rates of disease. However, because of different prevalence rates among people of the same race in different geographical locations, a clear conclusion cannot yet be drawn. The regional variation in the presentation of SLE is related to different genetic and the diversity of environmental influences[7].

The following studies were selected for comparison with our results: from the Middle East; Lebanon[8,9], Kuwait[10], United Arab Emirates (UAE)[11], Saudi Arabia[12,13,14], Jordan[15], from Asia; Pakistan[2,16] and Thailand[17], from Africa; Tunisia[18] and South Africa[19] and a multicentre study from Europe[20]. In this study, female to male ratio was found to be 20.8:1. This ratio is similar to what was seen in Jordan[15]. However, the ratio is higher compared to other studies; United Arab Emirates (UAE) was the only exception[11].

The mean age was found to be 31.89 years. This is similar to the pattern seen in Pakistan[2], Kuwait[10], Europe[20], Tunisia[18] and Makkah, Saudia Arabia[12]. However, it differs from that of Lebanon[8], United Arab Emirates (UAE)[11], Saudi Arabia[13,14] and Jordan[15] where the median age of the disease was lower but it was found to be higher in South Africa[19]. The reason for this discrepancy is not obvious.

In our study, all patients were Sudanese. Eighty-two (94.3%) were Arabs with Nubian (Kushite) ancestry and only five (5.7%) were non-Arab Black Africans (Nuba tribes). We observed from this study and with personal communication the virtual non-existence of SLE in Sudanese non-Arab Black Africans in the South (Nilotics mainly Dinka, Shuluk and Neur tribes) and Westerners (mainly Fur and Zagawa tribes). This observation is partially supported by Symmons[21], who reported rarity of SLE in West Africa and increased frequency in Central and Southern Africa. He attributed this to a possible protective effect of malaria, and he proposed that immigrants to United States (USA) develop the disease as they are not exposed to malaria. However, the protective malarial hypothesis of Symons's will not explain the situation here as malaria is endemic in the region of these ethnic groups as well as in other parts of the Sudan[22]. Symmons also postulated that the longer duration of immigration of African tribes to the states of America resulted in genetic admixtures. This change in genetic map predisposed black Americans to the disease, an explanation which appears to be compatible with our findings in relation to the role of genetic factors versus other factors in pathogenesis of lupus. However, in South Africa[19] the disease is more common in black subjects compared to mixed races, Asian and Caucasian. We believe that this virtual non-existence of lupus in some groups of Sudanese patients strongly support the pivotal role of genetic factors in the etiology of the disease compared to other triggering factors. In this study, we were unable to investigate the role of socio-economic conditions and residence (urban vs. rural). The effects of civil war, tribal conflicts and displacement made this rather difficult. However, studies from the USA had shown that these factors have an impact on the outcome[23].

The constitutional symptoms and family history patterns in our patients were virtually similar to other studies[18].

Around 40% of our patients experienced exacerbations interspersed with periods of

relative quiescence. Inadequacy of state health services, cultural factors and the cost of travel across long distances in a big country like Sudan, are among factors that are likely to contribute to the delay in early detection of SLE and hence have an impact on the outcome.

History of repeated abortions was only found in nine (10.8%) female patients and DVT in four (4.6%) however, these cases did not fulfill antiphospholipid syndrome (APS) criteria.

Higher frequency of malar rash in our patients is comparable to Tunisia[18] and South Africa[19], but is clearly higher than in Europeans[20], Pakistan[2] and Arabs[12,8,10,13,15,11,14]. This difference may be attributed to holo-seasonal sunshine in Sudan. Photosensitivity and discoid rash were nearly the same as that reported in above mentioned series (Table 1), but higher than that in found Pakistan[2]. Oral ulcers were more frequent in our study compared to others. This could be explained by associated poor oral hygiene and/or vitamins deficiencies. Most of our SLE patients were frequently treated with chloroquine either empirically or for established diagnosis of malaria, a practice which may result in a lichenoid drug eruption.

In our study, the frequency of neuropsychiatric disorders (Table 1) and hematological abnormalities (Table 2) appeared lower than in the other studies. We were unable to explain these findings. However, genetic and environmental factors are possible causes.

The frequency of serositis in our patients was nearly similar to that reported from Lebanon[8] and United Arab Emirates (UAE)[11], but lower than in Riyadh, Saudi Arabia[13] and higher than in other series. This variation could be related to the different tools of investigations, means of evaluation and interpretations of the results; however, it may also be a genuine difference in pattern of disease.

Nephritis is the most important predictor of outcome in SLE. Renal manifestations of SLE are variable in clinical presentation and prognosis, ranging from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis leading to acute renal failure. High frequency of renal involvement in the present study (63.2%) is similar to that seen in Saudi Arabia[13], and higher than in other studies. Renal involvement in SLE is almost invariable as shown by studies of adequate tissue biopsies which showed abnormal histopathology or immune deposits even in the absence of urinary abnormalities[24,25]. A possible additional contributory factor is bias of recruitment as patients were being looked after in nephrology units. The most frequently reported renal abnormalities in this study were hematuria and active urine sediments. Normal renal function, acute renal failure and end stage renal disease required dialysis were found in 69%, 24%, and 7% patients respectively. This had not been considered in most of the studies from Saudi Arabia[13,14].

The most frequent histologic pattern was class 4 lupus nephritis (WHO classification) a finding similar to studies from Lebanon[9], Pakistan[2,16], South Africa[19] and Riyadh, Saudi Arabia[13]. However, reports from Makkah, Saudi Arabia[12], Kuwait[10] and South Africa[19] indicated that the commonest class was WHO histological class 3. Studies from Tunisia[18] reported similar frequencies in both class 3 and 4.

The profile of antibodies (ANA and anti-DNA antibodies) in Sudanese patients (Table 4) showed remarkable variation in frequency between different studies. It is possible for a patient to have low levels of circulating antibodies (ANA) that may be too weak to be detected. Moreover, ANA

tests were performed by indirect immunofluorescence method wherein the patients' sera were incubated with mouse kidney / stomach / liver substrate. Human cell lines substrates are more sensitive and specific. This could explain some of the ANA negativity. Variations in anti-dsDNA antibody finding may be related to SLE activity among patients.

When comparing gender variation, male patients were found to have no discoid rash and hematological disorders. They were also found to have less oral ulcers. All male patients had arthritis. Photosensitivity, serositis, renal involvement and neuropsychiatric manifestation were more common in males compared to female patients, whereas skin rash was similar in both sexes. Antinuclear antibody was positive in all males and anti-dsDNA was more common among them (75% vs. 50.6%). Mongkoltanatus J et al[17] from Thailand reported lower prevalence of arthralgia, photosensitivity and neuropsychiatric manifestation in male. Also they had more prevalence of thrombocytopenia, discoid rash and renal insufficiency. Skin rash and hematological involvement was similar in both males and females.

Sudan has two distinct major cultures – Arabs with Nubian (Kushite) ancestry and non-Arab Black Africans[26]. In this study, SLE seems to predominantly affect the Afro-Arab group of the Sudan. The clinical features appeared to be similar to that reported in the literature.

We believe that lupus is underreported in Sudan, a situation that has led to unfounded belief that SLE is a rare disease in Sudan.

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