SYSTEMIC LUPUS ERYTHEMATOSUS IN LIBYANS: AN APPRAISAL OF THE 1982 REVISED CRITERIA FOR CLASSIFICATION

A. S. M. GIASUDDIN
I. A. SHAAFIE
M. N. KHAZI
M. M. ZIU

SUMMARY : The 1982 revised criteria for classification of systemic lupus erythematosus (SLE) was evaluated in 22 Libyan patients with SLE (age: 12-45 years; sex: 2 males, 20 females). Of these patients, 14 presented with idiopathic SLE, 2 with drug-induced SLE, 4 with hematological disorders and 2 with neuropsychiatric problems. In addition, 22 patients with classical features of rheumatoid arthritis (age: 14-50 years; sex: 5 males, 17 females), 10 patients with confirmed diagnosis of chronic active hepatitis (age: 18-52 years; sex: 4 males, 6 females) and 22 healthy Libyans (age: 12-55 years; sex: 6 males, 16 females) were included in the study for comparison with SLE. The 1982 revised criteria demands that at least 4 or more of the criteria be full-filled by a patient to be classified as having SLE. Each of our SLE patients fulfilled more than 4 or the 1982 revised criteria, although the predominant clinical features were arthralgias, malar rash, serositis and renal involvement. Of the various immunological investigations that were conducted and compared, anti-dsDNA antibody test exhibited the highest specificity for differential diagnosis of SLE. We, therefore, recommend the measurement of anti-dsDNA antibody in all cases wherever clinically appropriate regardless of the presence or absence of antinuclear antibody. The availability of anti-dsDNA test seems to be helpful in diagnosing SLE at an early stage of the disease the potential benefits of which are obvious.

Key Words: Systemic lupus erythematosus, anti-dsDNA antibody.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem disease of uncertain aetiology with variable clinical features and prognosis. While the 'false positive' serological test for syphilis was the earliest recognized immunological abnormality in SLE, the discovery of LE-cell phenomenon by Hargreaves *et al.* (8) and the identification of antinuclear antibody by Miescher *et al.* (15) led to the recognition of SLE as an immunological mediated disease. Subsequently, the discovery of auto-antibody to double-stranded DNA (anti-dsDNA) in SLE was reported almost simultaneously by many investigators (4, 18). It is subsequent application to the diagnosis and management of SLE has led to a greater recognition of the milder cases of the disease and to a marked increase in its reported frequency (11, 16, 17). Although anti-dsDNA auto-antibody was originally thought to be specific for SLE (11, 16), it has been shown to occur in about 20% of patients with chronic active hepatitis (6). Occasionally non-SLE sera from patients with Sjogren's syndrome, Felty's syndrome, discoid SLE and drug-induced lupus do show significant dsDNA-binding (9, 12, 13). In 1971 a subcommittee of the American Rheumatism Association (ARA) published a report on Preliminary Criteria for the classification of Systemic Lupus Erythematosus (5). These first criteria for the classification of patients with this disease were widely accepted and have been used as the basis for

*From Departments of Laboratory Medicine and Internal Medicine, Al-Arab Medical University, Benghazi, Libya.

Table 1: The clinical and laboratory findings in 22 Libyan patients with SLE as classified according to the 1982 revised criteria.

Patients		The 1982 revised criteria**										
Age/Sex	SLE-type*	A	B	C	D	E	F	G	H	I	J	K
12/F	SLE-I	+	-	-	+	+	+	-	-	-	+	+
14/F	SLE-I	+	-	-	+	+	-	-	-	-	+	+
25/F	SLE-I	+	-	-	+	+	-	+	+	-	+	+
18/F	SLE-I	+	-	-	-	+	-	+	-	-	+	+
22/F	SLE-I	+	-	-	-	+	-	+	+	-	+	+
19/F	SLE-I	+	-	-	-	+	+	+	-	-	+	+
14/F	SLE-I	+	-	-	-	+	-	+	-	-	+	+
25/F	SLE-I	+	-	-	-	+	+	-	-	-	+	+
20/F	SLE-I	+	-	-	-	+	+	-	+	-	+	+
35/F	SLE-I	+	-	-	-	+	+	-	+	-	+	+
30/F	SLE-I	+	-	-	-	+	+	+	+	-	+	+
35/F	SLE-I	+	-	-	-	+	+	+	-	+	+	+
28/F	SLE-I	+	-	-	-	+	-	+	-	+	+	+
16/F	SLE-I	+	-	-	-	+	-	+	-	+	+	+
12/F	SLE-H	-	-	-	-	+	+	-	-	+	+	+
18/F	SLE-H	-	-	-	-	+	+	-	-	+	+	+
21/F	SLE-H	-	-	-	+	+	-	-	-	+	+	+
45/F	SLE-H	-	-	-	-	+	+	-	-	+	+	+
41/F	SLE-P	-	+	-	-	-	+	+	+	+	+	+
27/F	SLE-P	-	+	-	-	+	+	+	+	+	+	+
35/F	SLE-D	+	-	+	-	+	-	+	-	-	+	+
45/M	SLE-D	+	-	+	-	-	-	+	-	+	+	+

* SLE-I: SLE-idiopahtic, SLE-H: SLE with hematological disorders, SLE-P: SLE with psychiatric problems, SLE-D: SLE-drug induced.
** A: Malar rash, B: Discoid lupus, C: Photosensitivity, D: Oral ulcers, E: Arthralgias, F: Serositis, G: Renal disorders, H: Neurological disorders, I: Hematological disorders, J: Immunological disorders, K: Antinuclear antibody, +: Presence, -: Absence

classification of patients in many clinical reports since that time (2, 21). However, the 1971 preliminary criteria did not incorporate immunological tests currently widely used in diagnosis and management of SLE. The subcommittee appointed in 1979 by ARA updated and revised these preliminary criteria incorporating the immunological tests, e.g. antibody to dsDNA, antinuclear antibody, LE-cell phenomenon etc, which was published in 1982 (20). When both the preliminary and revised criteria were compared, the 1982 revised criteria showed much improved sensitivity (96%) and specificity (96%) (5, 20). Literature survey indicated that there has been no reported work on the clinical and immunological aspects of SLE in Libyans. We have therefore planned the present study on Libyan patients with SLE. Some patients with rheumatoid arthritis (RA) and chronic active hepatitis (CAH) and healthy volunteers as controls (CS) were also included in the study for comparison.

MATERIALS AND METHODS

Patients

Twenty two patients, 2 males and 20 females in the age group varying from 12-45 years (mean age: 25 years), with the diagnosis of SLE were included in the study. Of these, 14 patients belonged to idiopathic-SLE, 2 to drug induced-SLE, 4 were diagnosed after treatment for sometime for hematological disorders, and 2 suffered from neuropsychiatric problems. The patients with idiopathic-SLE presented with a varying clinical picture of arthralgias, renal and neurological involvement. One patient with drug induced-SLE was being treated for endometrial tuberculosis and received isoniazid, rifampicin and ethambutol irregularly for 3 years when she developed features of SLE. Another patient with essential hypertension received hydralazine, 200 mg daily, for 3-4 years before developing features of SLE. The patients with hematological problems had idiopathic thrombocytic purpura (ITP) like picture (2 cases), pancytopenia (1 case) and autoimmune hemolytic anemia (1 case). One of the patients with ITP underwent spleenectomy and received steroids for 3 years before showing features of SLE. One of the patients with neurological problems started with vague pain in abdomen and vomiting, developed severe pain in leg with no evidence of deep vein thrombosis or joint inflammation and finally developed right sided lower motor neuron type of facial palsy with partial recovery. Another patient who was diagnosed as a case of SLE for 3 years and was receiving prednisolone (30 mg daily) and immuran (100 mg daily) got admitted with fever and abnormal behavior, became drowsy, developed convulsion, went into coma and finally died. The clinical and laboratory features of all 22 patients are classified according to the 1982 revised criteria for SLE (20) as shown in Table 1. In addition, 22 patients (5 males, 17 females; 14-50 years of age) with classical clinical and laboratory features of rheumatoid arthritis (RA), 10 patients (4 males, 6 females; 18-52 years of age) with confirmed diagnosis of chronic active hepatitis (CAH) and 22 healthy volunteers (age: 12-55 years, sex: 6 males, 16 females) were included in the study for comparison with SLE for some of the immunological parameters as stated in Table 2.

Table 2: The results of immunodiagnostic tests in patients (SLE, RA, CAH) and controls (CS).

Patients and Controls	ANA TEST		Anti-dsDNA antibody test		Rheumatoid factor		C-reactive protein	
	Positive (%)	Negative (%)	Positive (%)	Negative (%)	Positive (%)	Negative (%)	Positive (%)	Negative (%)
SLE	22 (100)	0 (0)	22 (100)	0 (0)	2 (9)	20 (91)	16 (73)	6 (27)
RA	5 (23)	17 (71)	0 (0)	22 (100)	21 (96)	1 (4)	21 (94.5)	1 (45)
CAH	2 (20)	8 (80)	0 (0)	10 (100)	0 (0)	10 (100)	2 (20)	8 (80)
CS	3 (16)	19 (84)	0 (0)	22 (100)	0 (0)	22 (100)	0 (0)	22 (100)

ANA: Antinuclear antibody, dsDNA: Double-stranded deoxyribonucleic acid, SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis, CAH: Chronic active hepatitis, CS: Control subjects

Assay of Anti-nuclear Antibody (ANA)

The ANA was assayed by immunofluorescence technique using rat kidney tissue slices as the source of nucleus (10). The FITC-labeled anti-immunoglobulin reagent used in visualizing ANA was obtained from Dakopatt, Denmark.

Assay of Anti-dsDNA Antibody

The radio-immunoassay kit from Amersham, England was used for quantitative determination of anti-dsDNA antibodies in serum. The Amersham Kit is based on the highly sensitive ammonium sulphate precipitation assay first described by Wold *et al.* (22). The intra-assay and inter-assay coefficients of variation were less then 10%. The results were expressed as 'units/ml'.

Detection of Rheumatoid Factor (RF) and C-Reactive Protein (CRP)

The presence of RF and CRP in serum were determined by the latex agglutination tests using diagnostic kits from bioMeriux, France. The serum specimens were assigned as 'positive' or 'negative' according to the criteria laid down in these commercial kits for routine use in diagnostic immunology laboratory.

Determination Of Immunoglobulins (IgG, IgA, IgM, IgD) and Complements (C3, C4)

The serum levels (mg/dl) of IgG, IgA, IgM, IgD, C3 and C4 were estimated by radial immunodiffusion (RID) technique using RID-Kits from bioMeriux, France as reported earlier (7).

RESULTS

The clinical and laboratory features in Libyan patients were classified according to the 1982 revised criteria and are shown in Table 1. All our patients fulfilled more than four of the 1982 revised criteria for diagnosis of SLE.

The results of some of the immunological tests in SLE-patients were compared with those of RA, CAH and CS (Table 2). The anti-dsDNA antibody test exhibited highest sensitivity and specificity for the classification of patients as having SLE.

The ranges of serum anti-dsDNA antibodies were 2-31 units/ml in CS, 50-400 units/ml in SLE, 2-32 units/ml in RA and 4-25 units/ml in CAH (Figure 1).

The results of the estimation of serum levels of IgG, IgA, IgM, IgD, C3, C4 are stated in Table 3. The levels of IgG and IgA were significantly raised whereas the levels of C3 and C4 were severely depressed in SLE compared to CS ($p<0.05$).

DISCUSSION

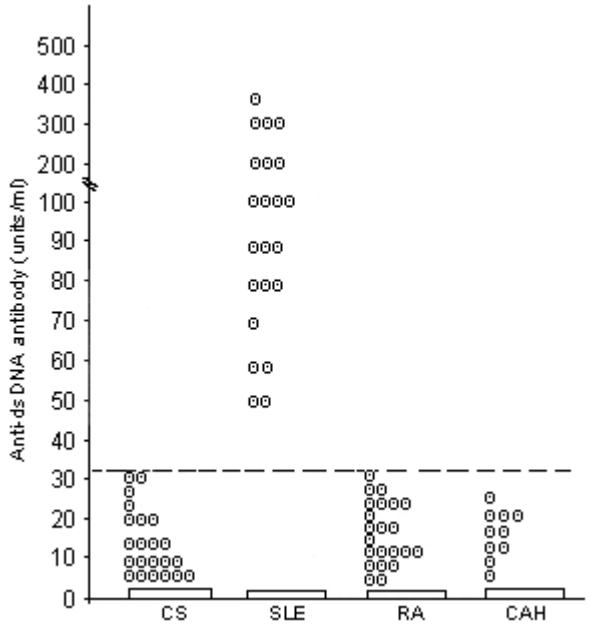
The 1982 revised criteria demands that at least 4 or more of the criteria be fulfilled by a patient to be classified as having SLE (20). Each of our patients fulfilled more than four of the 1982 revised criteria (Table 1).

Table 3: The serum immunoglobulin and complement levels in SLE and CS and their statistical comparison by student's t test.

	Serum immunoglobulins and complement levels* (mg/dl, mean±SD)					
	IgG	IgA	IgM	IgD	C3	C4
SLE	2638±205	457±41	198±30	7.5±2.7	45±8	14±4
CS	1032±147	239±38	129±25	5.8±2.1	128±20	35±11
SLE vs CS* (p value)	S	S	NS	NS	S	S

IgG: Immunoglobulin G, IgA: Immunoglobulin A, IgM: Immunoglobulin M, IgD: Immunoglobulin D, C3: Complement C3, C4: Complement C4, S: Significant ($p<0.05$), NS: Not significant ($p>0.05$).

FIgure 1: The serum anti-dsDNA antibody levels in patients (SLE; RA; CAH) and controls (CS).



The predominant clinical features in our patients were arthralgias, malar rash, serositis and renal involvement. However, the criteria 'J' (immunological disorders) and 'K' (antinuclear antibody) were positive in all our SLE-patients. Some of these immunological tests were, therefore, compared among CS, SLE, RA and CAH as stated in Table 2. Of the four tests that were compared, anti-dsDNA antibody test showed the highest specificity in making differential diagnosis of SLE. Of the 10 patients with CAH, 2 (20%) were positive for ANA-test, although all of them (10/10, 100%) were negative for anti-dsDNA antibody. This was in contradiction to a report that 42% (15/36) of CAH-patients had significant levels of anti-dsDNA antibody (6). The source of antibodies to dsDNA in their CAH-patients was difficult to explain, although one possibility was that it may be virus-induced as suggested by Talal (19).

None of our CS and RA-patients were positive for anti-dsDNA antibody suggesting high specificity and discriminating power of this immunological test for SLE. None of our SLE-patients were negative either for ANA in contrast to a report that 58% (22/38) of ANA-negative patients had SLE clinically and had significant ds-DNA binding capacity (14). Regarding the results of serum immunoglobulins and complements (Table 3), the rise in IgG and IgA and depression in C3 and C4 levels are consistent with many reports (1, 3, 13). The ARA-subcommittee analyzed in detail whether serum complement (C3, C4) determinations should be incorporated into the 1982 revised criteria set. After multiple computer analyses, they were unable to improve accuracy by using any combination of serum complement determinations, either as a separate criterion or by adding those determinations into one of the other combined variables. The clinical significance of serum complement determinations might, however, reside in their ability to assist in judging new and impending clinical events rather than in the process of initial diagnosis or classification.

In conclusion, our study showed that the anti-dsDNA antibody test has high specificity for differential diagnosis of SLE. Due to availability of this laboratory investigation there has been increased report of the prevalence of SLE throughout the world. Advanced renal disease is now less common due, in part, to the recognition of milder forms of the disease (17). Thus, the potential benefits of making the correct diagnosis of SLE at an early stage are obvious. We, therefore, recommend the measurement of anti-dsDNA antibody wherever clinically appropriate regardless of the presence or absence of anti-nuclear antibody.

REFERENCES

1. Blaese MR, Grayson J, Steinberg AD : Increased immunoglobulin-secreting cells in the blood of patients with active systemic lupus erythematosus. Am J Med 69: 345-350, 1980.

2. Canoso JJ, Cohen AS : A review of the use, evaluations and criticisms of the preliminary criteria for the classification of systemic lupus erythematosus. Arthr Rheum 22:917-921, 1979.

3. Cass RM, Mongan ES, Jacox RF, Vanglon H: Immunoglobulins G, A and M in systemic lupus erythematosus: Relationship to serum complement titre, latex titre, antinuclear antibody and manifestations of clinical disease. Ann Int Med 69:749-757, 1968.

4. Cepellini R, Polli C, Celada F: A DNA-reacting factor in serum of a patient with Lupus erythematosus diffusers. Proc. Soc Exp Biol Med 96:572-576, 1957.

5. Cohen AS, Reynolds WE, Franklin EC, Kulka JP, Roper MW, Shulman LE, Wallace SL : Preliminary criteria for the classification of systemic lupus erythematosus. Bull Rheum Dis 21:643-648, 1971.

6. Davis P, Read AE : Antibodies to double stranded (native) DNA in active chronic hepatitis. Gut 16:413-415, 1975.

7. Giasuddin ASM, Ziu MM, Basha SA, Abusedra A: Serum immunoglobulin and complement profiles in bronchial asthma in Libyans. J Islam Acad Sci 2(2):118-125, 1989.

8. Hargreaves MM, Richmond H, Morton R : Presentation of two bone marrow elements: the 'tart' cell and the 'LE' cell. Proc Mayo Clin 23:25-30, 1948.

9. Hess E : Drug-related lupus. N Eng J Med 318(22): 1460-1462, 1988.

10. Hudson L, Hay FC: Practical Immunology, 2nd Edition, Oxford: Blackwell Scientific Publications, 1980.

11. Hughes GRV, Cohen SA, Christian CL : Anti-DNA activity in systemic erythematosus: a diagnostic and therapeutic guide. Ann Rheum Dis 30: 259-264, 1971.

12. Lackmann PJ, Peters DK (eds): Clinical Aspects of Immunology, 4th edition, Oxford: Blackwell Scientific Publications, pp. 1305, 1983.

13. McCune WJ, Golbus J, Zeldes W, Bohlke P, Dunne R, Fox DA : Clinical and immunological effects of monthly administration of intravenous cyclophosphamide in severe systemic lupus erythematosus. N Eng J Med 318(22):1423-1431, 1988.

14. McHardy KC, Horne CHW, Rennie JAN : Antinuclear antibody -negative systemic lupus erythematosus- how common? J Clin Path 35:118-1121, 1982.

15. Miescher P, Fauconnet M, Berand T : Experimental immunonucleophagocytes and the LE phenomenon. Exp Med Surg 11:173-177, 1953.

16. Pincus T, Schur PH, Rose JA, Decker JL, Talal N: Measurement of serum DNA-binding activity in systemic lupus erythematosus. N Eng J Med 281: 701-705, 1969.

17. Ridley MG, Long PJ, Hughes GRV : Survival in systemic lupus erythematosus. Brit J Hosp Med 39(3):237-241, 1988.

18. Robbins WC, Holman HR, Deicher H, Kunkel HG: Complement fixation with cell nuclei and DNA in Lupus erythematosus. Proc Soc Exp Biol Med 96:575-579, 1957.

19. Talal N : Immunologic and viral factors in the pathogenesis of systemic lupus erythematosus. Arthr Rheum 13: 887-894, 1970.

20. Tan EM, Cohen AS, Fries JF, Masi AT : The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthr Rheum 25(11):1271-1277, 1982.

21. Trimble RB, Townes AS, Robinson H, Kaplan SB, Chandler RW, Hanissian AS, Masi AT : Preliminary criteria for the classification of systemic lupus erythematosus (SLE): evaluation in early diagnosed SLE and rheumatoid arthritis. Arthr Rheum 17:184-188, 1974.

22. Wold RT, Young FE, Tan EM, Farr RS: Deoxyribonucleic acid antibody: a method to detect its primary interaction with deoxyribonucleic acid. Science 161: 806-807, 1968.

Correspondence:
A. S. M. GIASUDDIN
Assistant Professor of Immunology,
Dept. of Laboratory Medicine,
Al-Arab Medical University,
P. O. Box-17383,
Benghazi, LIBYA.