Immunological Markers and Clinical Features with Systemic Lupus Erythematosus in Iraqi Women Patients

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التحري عن المعلمات المناعية والاعراض السريرية لمرضى داء الذئبة الاحمراري بين النساء العراقيات المصابات

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Abstract

Background: Systemic Lupus Erythematosus is a complicated condition caused by the immune system attacking disease with unclear causes, affecting mainly women. It manifests with various symptoms and is diagnosed based on clinical and serological signs. **Aims**: To investigate the prevalence and the type of immunological and hematologic manifestations in SLE from pathologist's perspective. **Methods**: The study was done on 60 SLE patients and 60 controls from the Consulting Rheumatology Clinic in Baghdad Teaching Hospital in Baghdad City during the first half of the year 2024, from 25th January 2024 until 25th April 2024. **Results**: Marital state that has married more affected (66.7%). 95% of patients tested positive for the anti-nuclear antibody and the anti dsDNA antibody also showed a high rate of positivity 86.7%. Hb and ESR highly significant difference (P=0.001) compared between patients and controls. The Arthralgia and arthritis were most common clinical features observed in SLEDAI and included (85%). **Conclusions**: Anti-dsDNA is a common antibody responsible for active diseases. Arthralgia and arthritis are most affected by SLE disease.

Keywords: SLE, Autoantibodies, Antinuclear antibodies, Indirect immunofluorescence

Abbreviations

SLE: Systemic Lupus Erythematosus

ANA: Antinuclear antibodies

HEp-20: Human epithelial cell tumor line

ELISA: Enzyme-linked immunosorbent assay

IIFT: Indirect immunofluorescence tests

المستخلص

المقدمة: داء الذئبة الاحمراري هو مرض مناعي معقد غير معروف الاسباب ,النساء يصابون به بصورة اكثر. يمكن تشخيصة عن طريق العلامات السريرية والسيرولوجية . **الهدف**: دراسة تنبأ كميات المظاهر المناعية ومعلمات الدم لتقييم الحالة المرضية للنساء المريضات. **طريقة العمل**: اجريت الدراسة على (60) مريضة مصابة بداء الذئبة من العيادة الاستشارية في مستشفى بغداد وحدة امراض المفاصل و 60 امرأه سليمة في النصف الاول من عام 2024 للفتره من يوم 25 كانون الثاني الى يوم 25 نيسان . **النتائج**: المتزوجات من النساء المصابة كانت اكثر نسبة (66.7 ٪). نسبة (95 ٪) من المصابات كان لهن الاجسام المضادة للنواة ذات نتيجة ايجابية و الأجسام المضادة للحمض النووي المضاعف بنسبة (86.7 ٪) .اما قياس الهيموغلوبين و تحليل سرعة ترسيب كريات الدم الحمراء فكان ذات دلاله معنوية عالية (0.001) عند المقارنة بين المرضى والاصحاء . التهاب في المفصل أو مجرد ألم بالمفصل من دون وجود التهاب كانوا بنسبة(85 ٪) في تقييم نشاط المرض في وقت التقييم. **الاستنتاجات**: الأجسام المضادة للحمض النووي المضاعف اكثر شيوعا في قابلية نشاط المرض. آلام المفاصل قد يكون بوجود الالتهاب او بدونه هو اكثر تأثيرا.

الكلمات المفتاحية: داء الذئبة الاحمراري ، الأجسام المضادة الذاتية، الأجسام المضادة للنواة، المناعة غير المباشرة بواسطة الصبغة الفلورية.

Introduction

Systemic lupus erythematosus is an autoimmune disease that is not well understood cause. Mostly seen in women, it presents with a range of symptoms (Emorinken *et al.*, 2021). It is identified by clinical and serological signs that, although distinctive, are insufficient to meet the classification criteria (Piga *et al.*, 2023). It is more prevalent among women than men at a ratio of 9:1 and is frequently seen in the age group of 15-40 years (Barber *et al.*, 2021). The frequency of SLE is between 72.1 and 74.4 per 100,000 individuals, with annual incidence rates of 5.6 per 100,000 individuals in predominantly Caucasian and African-American groups. African Americans experience elevated rates, while the disease is more common among Asian and Hispanic populations in comparison to Caucasians. The disease typically appears at a younger age and is more noticeable in African Americans (Tsai *et al.*, 2022). Linked to genetic and environmental influences such as viral infections and medications, triggering the creation of particular autoantibodies. The autoantibodies combine with autoantigens to create immunocomplexes that are then deposited in capillaries, resulting in systemic damage (Gong *et al.*, 2023). That affects numerous tissues and organs (Hasegawa *et al.*, 2023). The most recent clinical guidelines introduced by the European League Against Rheumatism/American College of Rheumatology in 2019 mandated a positive antinuclear antibody titer of 1:80 or higher as an entry requirement (Lam *et al.*, 2023). The aim of this investigation is to study the prevalence and the type of hematologic manifestations in SLE from pathologist's perspective

Materials and Methods

The case-control study included 60 patients and 60 controls. The research was done from 25th January 2024 until 25th April 2024. The patient reports are based on the criteria set by the European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR). ANA detection and pattern determination were conducted through IIF using HEp-20. Additionally, an ELISA immunoassay was conducted using an Enzyme-linked immunosorbent assay (ELISA, Sunlongbiotech), and the antibodies of each sample were obtained. Statistical analysis the results of this research were translated into a computerized database structure. Statistical analysis was carried out using the Social Sciences (SPSS) version 26.0. Mean, SD were used to express variables. Cross-tabulation was utilized to investigate a relationship between 2 categorical variables. The significance of these associations was evaluated using the Chi-square test (X^2) test. MedCalc software is utilized for ROC analysis, measuring parameter differentiation between two groups. AUC determines the test value. ROC also helps compare parameters and find the optimal cutoff for sensitivity and specificity.

Result

Demographics of the study groups

Based on the demographics of the groups being studied, it was shown in Table (1) that a central percentage of patients with SLE fell within the age group of 25-34 year at (36.7%). About 93.3% of individuals were unemployed, while 31.7% had completed secondary education. Martial state that has married more affected (66.7%). Furthermore, 31.7% of the individuals had a normal body mass index.

Table 1: Demographical characteristics of the study groups

Parameters study		Patients (N=60)		Controls (N=60)	
		No.	%	No.	%
Age (Year)	15-24	15	25.0	20	33.3
	25-34	22	36.7	16	26.7
	35-44	14	23.3	15	25.0
	45-55	9	15.0	9	15.0
Residency	Urban	50	83.3	52	86.7
	Rural	10	16.7	8	13.3
Occupation	Employed	4	6.7	8	13.3
	Unemployed	56	93.3	52	86.7
Martial state	Single	17	28.3	28	46.7
	Married	40	66.7	30	50.0
	Divorced	3	5.0	2	3.3
Education	Illiterate	2	3.3	4	6.7
	Primary	15	25.0	18	30.0
	Intermediate	7	11.7	10	16.7
	Secondary	19	31.7	8	13.3
	College	17	28.3	16	26.7
	High college	0	0	4	6.7
BMI	Under Weight	5	8.3	0	0.0
	Normal	19	31.7	32	53.3
	Over Weight	15	25.0	12	20.0
	Obese	17	28.3	14	23.3
	Extremely Obese	4	6.7	2	3.3

Prevalence of autoantibodies

95.0% of 60 patients showed a positive result for the ANA. Additionally, the anti-dsDNA antibody showed a high positive rate of 86.7%, with anti-SSA following at 51.7%, anti-Sm at 45.0%, anti-RNP at 16.7%, anti-SSB at 15.0%, anti-Scl-70 at 13.3%, and anti-Jo-1 at 10.0%.

The anti-C3 antibody had a positive rate of 73.3% and C3 antibodies at 48.3%. This is shown in Table (2),

Table 2: Distributions of autoantibodies prevalence in the patient group

Parameters	Positive		Negative	
	No.	%	No.	%
ANA	57	95.0	3	5.0
Anti-dsDNA	52	86.7	8	13.3
Anti-SSA	31	51.7	29	48.3
Anti-SSB	9	15.0	51	85.0
Anti-Smith	27	45.0	33	55.0
Anti-RNP	10	16.7	50	83.3
Anti-Jo1	6	10.0	54	90.0
Anti-Scl-70	8	13.3	52	86.7
C3	44	73.3	16	26.7
C4	29	48.3	31	51.7

Laboratory investigation of study groups

Parameters like WBC count, Hemoglobin level, platelet count, lymphocyte count, monocyte count, neutrophils, eosinophil count, basophil count, and ESR were examined in both patients and controls for investigation purposes. Data shown as mean± SD demonstrated that there was a difference in the mean investigation parameters between SLE patients and the control group. Independent T-test statistical analysis demonstrated a significant disparity in Hb, Hct, ESR, CRP, and urine test (RBCs, pus cell, and Alb) between the healthy controls and SLE patients in the groups. Finally, the analysis of WBC, neutrophils, monocytes, eosinophils, basophils, and platelets, in the different groups revealed no significant variance, as shown in the Table 3.

Table 3: Investigations laboratory among different SLE groups

	Patient		Control		P-Value
	Means ± SD	SE	Means ± SD	SE	
Blood tests					
WBCx109/L	8.24±3.35	0.433	7.75±1.41	1.415	0.306
LYM%	25.96±11.44	1.477	29.93 ±6.15	0.794	0.020*
NEU%	62.46 ±16.88	2.180	61.16±8.74	1.129	0.598
MON%	6.04±2.17	0.281	6.15±2.02	0.261	0.783
BASO%	0.31±0.15	0.020	0.27±0.12	0.016	0.163
EOS%	1.31±1.17	0.152	1.30±1.49	0.192	0.986
HGB g/dl	11.35±1.66	0.215	12.85±0.40	0.052	0.001**
HCT %	35.43±4.98	0.643	37.74 ±0.71	0.092	0.001**
PLTx109/L	262.62±80.82	10.434	281.73±99.16	12.802	0.249
ESR mm/hr	42.75 ±28.01	3.616	10.53±4.44	0.574	0.001**
Urine tests					
RBC/µl	31.96 ±27.77	3.585	3.92±2.33	0.302	0.001**
WBC/µl	28.05 ±25.95	3.351	3.77±1.94	0.250	0.001**
PRO g/l	0.27±0.57	0.075	0.00±0.00	0.000	0.001**
Cast/µl	0.12±0.37	0.048	0.00±0.00	0.000	0.017*

SD: Standard Deviation; SE: Standard Error

Receiver operative curve of autoantibodies markers among SLE group

Receiver Operative Curve (ROC) analysis was also used to determine the optimal cutoff point for medical tests. Table (4) and Figure (1) demonstrate the cutoff where sensitivity and specificity values intersect, including critical levels for evaluating area parameters below fifty percent, with a 95% confidence interval pertaining to ANA testing., dsDNA, SS-A, SS-B, Sm, RNP, Scl-70, and Jo1 antibody markers within diagnosis SLE patients concerning. this is shown in Table (4).

Table 4: Correlation levels of biomarkers in the serum of SLE patients

Parameters	Cutoff Point	Area under curve (AUC)	Asymp. Sig.	Asymptotic 95%C.I.		Specificity	Sensitivity
				L.B.	U.B.		
ANA	37.3	0.974	0.0001**	0.927	0.994	100.0	95.00
dsDNA	22.0	0949	0.0001**	0.893	0.981	100.0	86.67
Anti-SS-A	17.7	0.765	0.0001**	0.679	0.837	100.0	51.67
Anti -SS-B	49.42	0.541	0.5163	0.432	0.646	100.0	15.00
Anti -Sm	28.9	0.711	0.0001**	0.621	0.790	100.0	45.00
Anti -RNP	32.2	0.501	0.982	0.394	0.609	100.0	16.67
Anti-Jo1	39.5	0.503	0. 9690	0.395	0.610	100.0	10.00
Anti Scl-70	45.2	0.522	0.7352	0.414	0.628	100.0	13.33

**:(**) Highly Sig. at P<0.01; C.I.: Confidence Interval; L.B.: lower bound; U.B.: upper bound

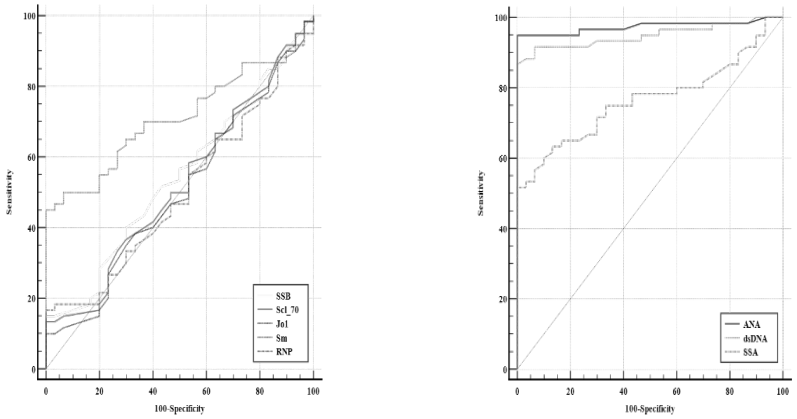

Figure (1): ROC Curve Chart for the association autoantibodies markers distributed of SLE group.

Clinical features of SLEDAI in SLE patients

The most common clinical components observed in SLEDAI included arthritis/arthralgia (85.0%), lupus headache (65.0%), fever (60.0%), new rash (56.7%), alopecia (48.3%), visual disturbance (46.7%), myositis (41.7%), mucosal ulcers (41.7%), pyuria (35.0%), vasculitis (20.0%), pleurisy (6.7%), pericarditis (6.7%), cranial nerve disorder (3.3%), CVA (3.3%), seizure (1.7%), with organic brain syndrome and psychosis at (0.0%) as shown in Figure (2).

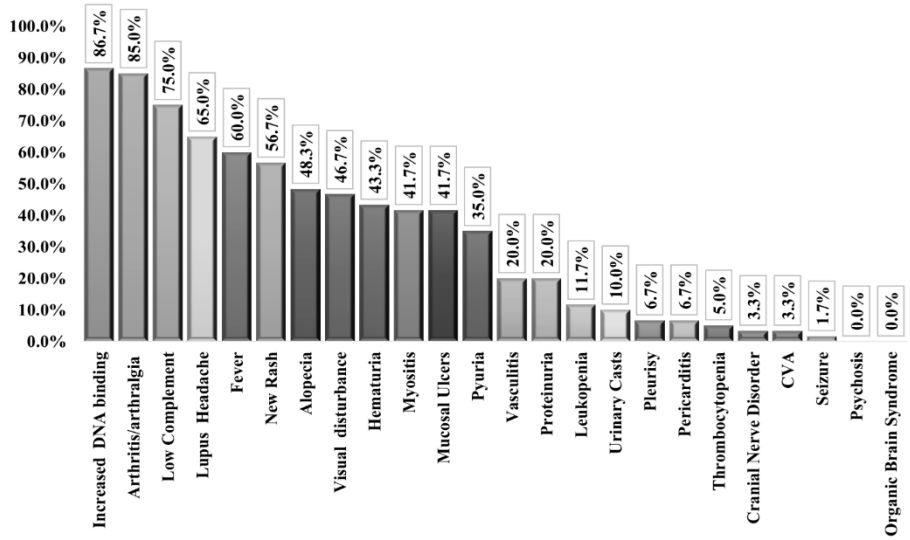

Figure (2). The frequency of SLEDAI clinical features components among 60 patients with SLE.

The association of autoantibodies with clinical manifestations of SLE

The relationship between various autoantibodies and clinical symptoms is summarized briefly in Table (5). Cranial nerve disorder showed a strong significance with anti-Jo1 (P=0.001). Myositis was linked to anti-RNP antibodies and C4 levels, with a correlation of P(0.026 and 0.029, respectively). Mucosal ulcers were associated with anti-dsDNA, and anti-SSA antibodies,

with P(0.010, 0.040, and 0.022 respectively). Arthralgia was correlated with anti-dsDNA antibodies, with a P value of 0.023. The occurrence of C3 (P=0.010) and C4 (P=0.002) were associated with an increased likelihood of developing Lymphadenopathy. Avascular necrosis showed a significant association with an anti-SSB antibody (P = 0.016) and C3 (P = 0.010). Furthermore, patients who had C4 (P = 0.045) were found to have developed Discoid lupus. The various autoantibodies had no correlation with other clinical symptoms.

Table 5: Correlation between clinical manifestations and autoantibodies among SLE group

clinical manifestations	ANA	dsDNA	SSA	SSB	Sm	RNP	Scl70	Jo-1
	P	P	P	P	P	P	P	P
Seizure	0.817	0.692	0.329	0.672	0.362	0.652	0.692	0.737
Visual disturbance	0.476	0.577	0.073	0.885	0.405	0.064	0.577	0.301
Cranial Nerve Disorder	0.741	0.573	0.137	0.546	0.193	0.520	0.121	0.001
Lupus Headache	0.950	0.339	0.244	0.909	0.765	0.069	0.873	0.417
CVA	0.741	0.573	0.962	0.546	0.193	0.520	0.573	0.055
Vasculitis	0.374	0.704	0.071	0.857	0.697	1	0.704	0.197
Arthritis	0.455	0.056	0.800	0.723	0.971	0.146	0.202	0.278
Myositis	0.764	0.072	0.315	0.582	0.895	0.026	0.797	0.029
New Rash	0.120	0.721	0.821	0.511	0.228	0.641	0.683	0.602
Alopecia	0.086	0.156	0.993	0.233	0.979	0.419	0.389	0.071
Mucosal Ulcers	0.764	0.010	0.040	0.199	0.693	0.412	0.797	0.190
Pleurisy	0.635	0.417	0.334	0.384	0.405	0.355	0.477	0.301
Pericarditis	0.057	0.417	0.945	0.384	0.835	0.355	0.417	0.490
Fever	0.809	0.163	0.752	0.238	0.916	0.157	0.088	0.725
Fatigue	0.400	0.601	0.379	0.123	0.169	0.881	0.647	0.221
Arthralgia	0.374	0.023	0.245	0.857	0.697	0.386	0.569	0.389
Lymphadenopathy	0.817	0.692	0.297	0.679	0.362	0.652	0.010	0.002
Avascular necrosis	0.817	0.692	0.329	0.016	0.362	0.652	0.010	0.737
Raynaud's phenomenon	0.844	0.822	0.204	0.718	0.708	0.522	0.286	0.504
Discoid lupus	0.554	0.129	0.931	0.278	0.795	0.248	0.129	0.045
Photosensitivity	0.327	0.905	0.451	0.104	0.668	0.172	0.905	0.684

Discussion

A higher proportion of patients resided in urban areas, primarily because the majority of samples were collected from Baghdad city. In these studies, autoantibodies similar to ANA, anti-dsDNA, anti-Sm, anti-SSA, and anti-SSB were identified with percentages of 90%, 85%, 32%, 65%, and 23%, respectively (Olferiev *et al.*, 2022). A high percentages of SLE may be consistently identified through the anti-ANA antibody (Anis *et al.*, 2023). Accurate identification and diagnosis of systemic lupus erythematosus requires specific testing for anti-dsDNA (Orme *et al.*, 2022). In this study discovered that the presence of the anti-dsDNA antibody correlated with disease activity, low white blood cell count, low red blood cell count, and elevated ESR levels, in line with earlier research (Correa-Rodríguez *et al.*, 2021). Kidney damage tends to lead to higher ESR levels, consequently reducing Alb levels. (Aringer, 2020). Anti-dsDNA and anti-Sm autoantibodies play a crucial role in the production of immune complexes and inflammatory damage on several organs, including the kidney, skin, and central nervous system (CNS). They are particularly specific to SLE (Lou *et al.*, 2022).

Within ANA testing, the anti-nuclear antibody assay holds greater diagnostic and prognostic significance. In systemic lupus erythematosus, the ANA test shows a sensitivity of 60-80% and an impressive specificity of 95-99%, giving it a strong predictive value. Autoantibodies can be detected in the early stages of SLE, including the preclinical phase (Li, H. *et al.*, 2022). this agrees with Jassim's study in ANA and dsDNA (with AUC 1.00, had a sensitivity and specificity of 100%), and the presence of double-strand DNA antibodies at a level of AUC ≥ 1.706 U/ml, had 100% sensitivity and 100% specificity) (Jassim *et al.*, 2023).

Amongst anti-dsDNA unlike with study (Homa-Mlak), In SLE, the anti-dsDNA assay has a sensitivity of 40.74% and a specificity of 81.25%, with no significant difference found (p=0.399) (Homa-Mlak *et al.*, 2022).

Anti-Sm is widely recognized as a marker antibody of SLE in retrospect. In contrast to the low sensitivity and high specificity typically seen in SLE diagnosis, anti-Sm had a specificity of 100.0% and sensitivity of 45.0% when detected by ELISA, indicating a strong positive predictive value for diagnosing SLE. Yet, the diagnostic usefulness for the majority of negative patients is restricted because of its high specificity. The finding in this result the Specificity for all markers are 100% this agrees with Li results in ANA (99.3), anti-ds-DNA(98.87%), anti-SSA(87.47%), anti-SSB(97.21%), anti-Smith(99.74%), and anti-RNP (99.56%) (Li, Hejun *et al.*, 2022).

Arthritis was the predominant clinical manifestation, observed in 85% of the individuals, which was also observed in other study (Metry *et al.*, 2019). SLE-related arthritis which it usually appears as non-erosive arthritis and was found in 51 out of 60 patients, closely matching our results. (85.0%) (Csóka *et al.*, 2024). Even though conditions such as arthritis or arthralgia are typically temporary, they can exhibit symptoms resembling those of rheumatoid arthritis (RA), such as long-lasting stiffness, swelling, pain, and decreased mobility. Though tendonitis or tenosynovitis may also be present, the metacarpophalangeal and interphalangeal, wrist, and knee joints are the most commonly afflicted (Ceccarelli *et al.*, 2022).

Hematologic abnormalities, including lymphopenia, anemia, and thrombocytopenia, are commonly found in SLE patients reflecting the activity of the disease over time. Anemia may result from lupus medication usage through either an idiosyncratic response or a dose-dependent mechanism

(Santacruz *et al.*, 2022). This finding agrees with Soliman's study of ESR and platelets. ESR evaluated in SLE patients (42.75±28.010) more than the control (10.53±4.447) similar to his study (39.4 ± 27.0),(7.8 ± 2.8), respectively and P=0.001. Platelets in SLE patients (262.62 ±80.820) while in control (281.73±99.168) and no significant, similar to his study (290.5 ± 100.6), (302.9 ± 93.4), respectively and P>0.05 (Soliman *et al.*, 2023).

SLE patients with anti-dsDNA positive were significantly higher in with Oral mucosal ulcer (Esquivel-Pedraza *et al.*, 2021 ; Xingguo *et al.*, 2008) and with Arthralgia or arthritis (Iaremenko and Koliadenko, 2022). Antibody levels are higher in SLE patients with positive anti-dsDNA antibodies compared to those with negative antibodies (P<0.05). Anti-Sm antibodies showed significant associations with serositis, renal involvement, psychosis, vasculitis, Raynaud's phenomenon, hemolytic anemia, leukopenia, lymphopenia, and arterial hypertension in the multivariable analysis. (Arroyo-Ávila *et al.*, 2015). In this study, there was no significant difference found for damage accumulation.

Conclusions

ANA and anti-dsDNA that commonest antibodies in SLE followed by anti-SSA and SSB. Anti-dsDNA is a commonest antibody responsible for active diseases. Arthralgia and arthritis are most affected by SLE disease. No association was found between auto antibodies and major clinical features.

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