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Does Rheumatoid Factor have any Protective Role in Patients with Lupus Nephritis

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that appears to result from an immune-regulatory disturbance caused by an interplay of genetic, hormonal, immunological, and environmental factors.
Objectives: To test the hypothesis that rheumatoid factor (RF) protects against lupus nephritis in Iraqi patients with SLE.
Materials and methods: Fifty-eight consecutive patients with SLE, who fulfilled the American College of Rheumatology (ACR) revised criteria for the diagnosis of SLE and attend the rheumatology unit of Baghdad Teaching Hospital during the period June 2000 to June 2001 were enrolled in the study. SLE patients divided into 2 groups (with lupus nephritis=30, without lupus nephritis =28) and a third group of control patients =30.
Results: All SLE patients with and without lupus nephritis had positive antinuclear antibodies. There were no obvious differences in the positivity rate of RF in SLE patients both with and without lupus nephritis (P-Value > 0.05). The disease activity was slightly higher in those with RF positives compared to those with RF negatives. The disease activity score was significantly higher in those with lupus nephritis compared to those with no lupus nephritis (p=0.007) .
Conclusion: RF appears to play no significant role in the protection of renal disease in Iraqi patients with SLE. The presence of RF in SLE patients is associated with a lower disease activity score. The presence of lupus nephritis is associated with a higher disease activity score.

Keywords: Systemic lupus erythematosus; Rheumatoid factor; Renal disease; nephritis.

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INTRODUCTION

The systemic lupus erythematosus (SLE) is a chronic inflammatory disease, which appears to result from an immune-regulatory disturbance brought by the interplay of genetic, hormonal, immunological, and environmental factors[1, 2]. The disease affects primarily young women. The highest incidence affects the age group 15-40 years but it may occur at any age group, with female to male ratio of approximately 5:1 [2, 3].

In Iraq, the prevalence of SLE is about 1/1867 of the general population and the first case of SLE was reported in 1971[4, 5]. Many immune defects occur in subjects with SLE and the cause of the disease remains obscure. Besides, we can't determine which defects are primary and which are secondary, some of these immune abnormalities are episodic and some correlate with the activity of the disease [2]. Renal disease is present in one half to two-thirds of patients, but there is a various degree of kidney injury that can be evaluated by clinical and more definitively by pathological examination [6]. The prevalence of lupus nephritis among SLE patients in Europe was up to 90 per 100000 [7].

According to the revised 1982 American College of Rheumatology (ACR) criteria for the diagnosis of SLE which consists of 11 criteria [8], the lupus nephritis consists of the following 1) Persistent proteinuria more than 0.5 g per day or more than 3+ if quantitation not performed. Or 2) Cellular cast (red cell, Hb, granular, tubular of mixed).

Rheumatoid factors (RF) are antibodies against the FC portion of IgG [9]. Several studies have suggested that RF

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protects against the development of renal disease in patients with SLE [10–14]. Demonstration of the reactivity of RF with soluble antigen-antibody immune Ag-Ab complexes to form more heavily sedimenting immune precipitates has led to the idea that it's may involve the formation of less soluble complexes, easily phagocytosed and thus less likely to deposit in renal glomeruli [15]. RF might also compete with complement for binding with immune complexes, thus minimizing their injurious properties [10].

Several studies showed contradictory results regarding how RF protects against the development of renal disease in patients with SLE. To the best of our knowledge, four studies showed no protective effects whereas four showed a protective effect. There are some possible reasons for the disparity between the results of these studies. Firstly, it reflects differences in assay methods. Most authors used the latex test, while others used red blood cells. The study by Louthrenoo et al. used the ELISA test and found a significant negative correlation between RF positive test and lupus nephritis [16]. Secondly, the small number of sample sizes studied may not pick up statistical significant differences.

We aimed to test the hypothesis that RF protects against lupus nephritis in Iraqi patients with SLE and to detect the possibility of their association with disease activity.

MATERIALS AND METHODS

Fifty-eight consecutive patients with SLE, who fulfilled 4 or more of 1982 ACR [8] revised criteria for the classification of SLE attending rheumatology unit of Baghdad Teaching Hospital, were included in this prospective study. SLE patients were divided into two groups : Group I: 30 patients with lupus nephritis, 25 of them were diagnosed with clinically + biopsy, and 5 were diagnosed clinically without a biopsy. Group II:28 lupus patients with no evidence of nephritis. A randomly selected sample of 30 patients with idiopathic renal disease studied as a control group.

A full history was taken from all patients, with special emphasis on symptoms of lupus nephritis and proper physical examination was done for all patients. Laboratory test includes general urine examination (GUE), renal function test, and 24 hour urinary protein. Complete blood count (CBC), erythrocyte sedimentation rate (ESR), complement (C3, C4), and autoantibodies like ANA, anti- ds DNA, and RF was done for all patients. RF is detected by latex agglutination test. Measurement of the disease activity performed by a standardized chart of the SLE disease activity index (SLEDAI)[17]. Informed consent was taken from all patients and controls for admission in the study. This study approved by the College Committee of Postgraduate Studies, College of the Medicine /University of Baghdad.

Data were converted into a computerized database structure. Statistical analyses were done using SPSS version 7.5 computer software (Statistical Package for Social Sciences). Frequency distribution for selected variables was done first. Categorical variables between the study groups were assessed by the Chi-squared test. When the criteria for a valid Chi-squared test were not fulfilled (small expected frequencies), Fisher's exact test was used. The statistical significance of the difference in mean of a certain dependent continuous variable between 2 study groups was assessed by the test. A P-Value less than the 0.05 level of significance was considered statistically significant.

RESULTS

The mean age of patients in the lupus nephritis group was 28±11.6 (age range 15-20) and 32.1±11.9 (age range 20-43.5) in lupus patients without nephritis. The mean age of the idiopathic renal disease group was 32.1±15.1 (age range 18-47). The highest age group affected in the lupus nephritis group was 40 years and more (36.6%), SLE with no evidence of nephritis group was 30-39 (39.3%), and in idiopathic renal disease group was <20 years (33.3%). Females were more affected in all study groups than males (83.3% in lupus group, 85.7% in SLE with no evidence of nephritis group, and 67.7 in idiopathic renal disease group) Table 1.

Three patients (10%) of the lupus nephritis group reported a positive family history of SLE while none of the lupus patients without nephritis had a positive family history (P-Value=0.13) Table 2.

More than half (53.6%) of lupus nephritis patients were treated by cytotoxic drugs, which is significantly higher than that for SLE patients without nephritis (13.3%) (p=0.004) Table 2.

SLE disease activity score (SLEDAI) was higher in SLE patients with nephritis than those with no evidence of nephritis. The proportion of SLE cases with a high risk of mortality was significantly higher among those with nephritis (96.7%) than those with no evidence of nephritis (64.3%) P=0.007 Table 3.

The mean SLEDAI score was significantly higher in those with nephritis (35.2) compared to those with no evidence of nephritis (27.8) P (X2) =0.007 as shown in Table 3.

Twenty percent of lupus nephritis and 21.4% of SLE patients without nephritis showed positive RF. The positivity rate of RF in both groups is comparable (P>0.05). All patients with and without nephritis had positive ANA. A significantly higher number of lupus nephritis patients had positive anti-ds-DNA (71%) compared to those without nephritis (39.3%) P-Value=0.02 Figure 1.

Regarding the pathological classification of lupus nephritis, 3 patients with diffuse proliferative type had RF. One patient

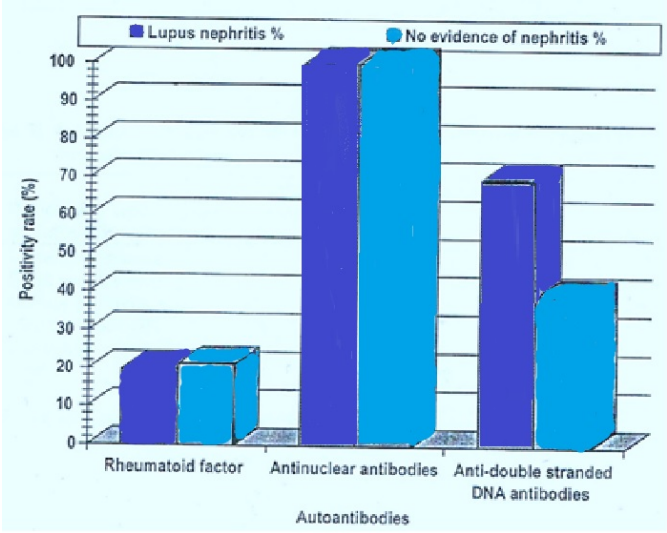

Figure 1. Bar chart showing the differences in positivity rate of selected autonatibodies in SLE cases in the presence and absence of nephritis.

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Table 1. The age and gender distribution of the study groups.

Variable	Study groups					
	SLE with Evidence of nephritis		SLE with no Evidence of nephritis		Idiopathic renal Disease	
	No.	%	No.	%	No.	%
Age groups (years)						
<20	9	30.0	5	17.9	10	33.3
20-29	8	26.7	6	21.4	3	10.0
30-39	2	6.7	11	39.3	9	30.0
40+	11	36.6	6	21.4	8	26.7
Total	30	100	28	100	30	100
Mean ± SD	28±11.6		32.1±11		31.2±15.1	
P-Value = 0.08						
Gender						
Female	25	83.3	24	85.7	23	67.7
Male	5	16.7	4	14.3	7	32.3
Total	30	100	28	100	30	100

Table 2. Frequency distribution of SLE patients by family history and drug therapy.

Variable	Study groups			
	Lupus nephritis		SLE with no evidence of nephritis	
	No.	%	No.	%
Family history of SLE				
Negative	27	90.0	28	100
Positive	3	10.0	0	0
P-Value = 0.13				
Drug therapy				
None	1	3.6	6	21.3
High dose steroids	8	28.6	9	32.0
Cytotoxic drugs	16	53.6	3	13.3
Combination of steroids and cytotoxics	5	14.3	10	33.3
P-Value = 0.004				
Total	30	100	28	100

Table 3. Frequency distribution of SLE cases in 2 study groups by the severity of the disease according to SLEDAI.

SLEDAI	SLE cases			
	Lupus nephritis		No evidence of nephritis	
	No.	%	No.	%
Mild to moderate	0	0	1	3.6
Severe	1	3.3	9	32.1
Risk of mortality	29	96.7	18	64.3
Total	30	100	28	100
P-Value = 0.007				

for each Mesangial and membranous glomerulonephritis also had RF. No statistically significant difference with all nephritis types concerning RF state (P-Value>0.05)Table 4

Musculoskeletal manifestations had the highest rate in the SLE patients with or without lupus nephritis (96.4% and 96.7 respectively). No statistically significant difference between the 2 groups regarding the SLE manifestations (P-Value>0.05), except the renal involvement which showed a high statistically significant difference between the 2 groups (P-Value=0.001) Table 5

There was a high statistically significant difference between the 2 groups (bleeding vs non-bleeding) regarding the number of platelets, PT, and APTT P-value 0.001 Table 6.

DISCUSSION

SLE is not as rare in Iraq as was previously thought. Our study shows female: male (5.6:1), while Al-Rawi et al study reported a female: male ratio of 4:1 [4]. A prior study reported a ratio up to (30:1) during childbearing years [13]. This may be linked to estrogen effect through the stimulation of T and B cells which in turn leads to more auto-antibodies production.

This study showed that the predominant age group for SLE patients is the reproductive years 30-39 years which is in agreement with the prior study [4], this may be explained by the role of interferon-alpha (IFN-) in the placenta, the influence of female sex hormones on IFN- and Toll-like receptor (TLR) expression, fetal and maternal microchimerism [9].

The present study showed a relation between lupus nephritis and the positive family history of SLE (3 patients out of 30). Pinillos found that the first degree relatives of patients with SLE are significantly more likely to have the disease compared with the rest of the population [13].

The present study paid special attention to clinical and laboratory markers and illustrate the disease activity by using SLEDAI which depends on a multitude of disease manifestations and gives different weights according to the importance of this specific manifestation. Baldwin et al [18] reported that the refined use of cytotoxic agents and careful monitoring of patients is higher among patients with lupus nephritis than among those without nephritis, this is following our study Table 2.

RF can present in the blood of a few percents of SLE patients. Hoffman et al[19] found that RF was positive in 13% of SLE patients (26 patients out of 201). Many studies were done about the effect of positive RF test on the disease activity and lupus nephritis [11, 20]. Tarkowski and Westberg found that positive RF is associated with low disease activity [11], while Turner Stokes [20] reported no such association. In

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Table 4. Association of pathological type of lupus nephritis with the presence of RF*.

Pathological type of lupus nephritis (biopsy results)	Rheumatoid factor (SLE nephritis)				Total		P-Value
	Negative		Positive				
	No.	%	No.	%	No.	%	
Mesangial disease	2	10.5	1	16.7	3	12.0	0.57
Focal proliferative	5	26.3	0	0	5	20.0	0.18
Diffuse proliferative	11	57.9	3	50.0	14	56.0	0.43
Membranous GN	0	0	1	16.7	1	4.0	0.27
Inconclusive	1	5.3	1	16.7	2	8.0	0.46
Total	19	100	6	100	25	100	

* 5 cases had no pathological typing.

Table 5. Difference in the positivity rate of different SLE manifestations between SLE cases with no evidence of nephritis and those with nephritis*.

SLE manifestations	SLE patients				
	With lupus nephritis		Without lupus nephritis		
	No.	%	No.	%	P-Value
Neurological	26	92.9	26	90.0	0.8
Musculoskeletal	27	96.4	27	96.7	0.7
Renal	30	100	11	36.7	0.001
Mucocutaneous	26	92.9	24	80.0	0.15
Serositis	2	7.1	1	3.3	0.47
Immunological abnormalities	16	57.1	22	73.3	0.198
Constitutional symptoms	20	71.4	18	60.0	0.36
Hematologic abnormalities	2	7.1	1	3.3	0.47
Total SLE cases	30	100	28	100	

* None had vasculitis.

our study, SLEDA score was slightly higher among those with negative RF compared to those with positive RF in group 1, this account either the presence of RF which is associated with less disease activity or an observed difference which is a chance finding (since the difference was insignificant). As RF was not associated with disease activity, the SLEDAI score was slightly higher among those with negative RF compared to those with positive RF in group 1.

Depending on biopsy results, the current study showed a high prevalence of class IV, III, and II and low prevalence of class I which might be attributed to high patient selection for biopsy by our nephrologist.

SLE is a systemic disease involving many systems such as skin, joints, muscles, blood, nervous system, immune system, and kidneys. SLE patients without lupus nephritis could have a renal disease as hematuria and mild protein urea. The current study showed that there was no statistically significant difference between SLE patients with and without nephritis regarding all the systems except the renal system involvement [P-Value = 0.001].

Several studies showed contradictory results regarding RF protects against the development of renal disease in a patient with SLE. To the best of our knowledge, there were four studies which showed no protective effect of RF [13, 15, 19, 20] whilst another four series showed a protective effect of RF [10, 11, 18, 21]. In this study, we have included more variables to look for the role of RF protection against lupus nephritis. We have included lupus nephritis, lupus without nephritis, control group, and disease activity measured by using SLEDAI. Our study, as well as Turner, stokes et al study [20] have included a control group which was idiopathic nephritis without evidence of autoimmune rheumatic diseases. There are some possible reasons for the disparity between the results of these studies.

Firstly it could reflect differences in assay methods. Most authors employed aggregation tests using either latex particles or red blood cells (Rose-Waaler test). The varying result was obtained with either method especially Hill et al [21] demonstrated a protective role when they use the RBC (Rose-Waaler test) method which was not achieved when latex test was used. A report from Pinillos et al [13] once again by using the RBC method found a protective effect and he suggested that differences in methodology could account for the discrepancies.

Secondly, the variable activity of renal disease could also account for observed differences [19]. Turner Stokes et al [20] studied patients both in (active and inactive phases of their disease and in addition to standard latex test they used an radio immune assay (RIA) which distinguish three isotypes of RF (IgG, IgM, IgA), they discovered no protection by RF. Tarkowski and Westberg [13] also measured RF isotype by RIA and reported a protective role for all three isotypes (IgG, IgM, IgA) against the development of lupus nephritis, as shown in Table 6.

In conclusion, RF appears to play no significant role in the protection of renal disease in Iraqi patients with SLE. The presence of lupus nephritis is associated with a significantly higher disease activity score. The disease activity was slightly higher among those SLE patients with negative RF compared to those with positive RF test. This study paid special attention to the importance of the specific manifestation (clinical and laboratory markers) as a measure of disease activity by using SLEDAI.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Table 6. Comparisons of previous studies with the present study.

Authors	Years	SLE defined	Number with SLE	Renal disease defined	Number with renal disease	Active, inactive phase studied	Assay method	Protective effect (P-Value)
Davis and Bollet [10]	1966	Not specified	35	Clinical	23	No	Not specific	< 0.001
Kantor et al [15]	1969	Clinical	51	Not specified	24	No	Latex	NS
Baldwin et al [18]	1970	Clinical + ANF or LE cells	82	Biopsy	27	No	Latex	NS
Hill et al [21]	1978	1971 ARA criteria	59	Biopsy	59	No	Latex> 1/80, RBC agglutination>1/32	>0.05-0.1 <0.05
Pinillos et al [13]	1987	1982 ACR criteria	78	Clinical+biopsy in (38)	40	No	RBC agglutination>1/64	NS
Tarkowski and Westberg [11]	1987	1982 ACR criteria	51	Clinical	25	Yes	RIA IgG IgA IgM	<0.001 <0.05 <0.05
Turner Stokes et al [20]	1989	1982 ACR criteria	51	Clinical+biopsy in (19)	26	Yes	Latex>1/40 RIA IgG IgA IgM	NS
Hoffman et al [19]	2005	1982 ACR criteria	13	Clinical	6	No	Latex	significant
Present Study	2002	1982 ACR criteria	58	Clinical+biopsy in (25)	30	SLEDAI	Latex	NS

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