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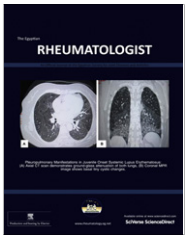

ORIGINAL ARTICLE

Anti-C1q and anti-dsDNA antibodies in systemic lupus erythematosus: Relationship with disease activity and renal involvement in Sharkia governorate, Egypt

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KEYWORDS

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Abstract *Introduction:* Renal involvement is one of the main determinants of poor prognosis of systemic lupus erythematosus (SLE). Kidney biopsy is an invasive procedure and accompanied by potential risks. Thus defining a reliable biomarker of kidney involvement in SLE is highly desirable.

Aim of the work: To assess the role of anti-C1q Ab in combination with anti-dsDNA Ab in detection of SLE disease activity and renal involvement (lupus nephritis).

Patients and methods: Anti-C1q Ab and anti-dsDNA antibodies were determined in 60 randomly selected adult SLE patients one of them refused the biopsy and those who completed the study were 59. The control group included 25 age and sex matched volunteers. According to

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lupus nephritis (LN) and SLEDAI score, patients were divided into four groups: group 1, 11 patients had active disease with LN; group 2, 20 patients had inactive disease with LN; Group3, six patients had active disease without LN; group 4, 22 patients had inactive disease without LN.

Results: A significant association of active lupus nephritis detection and the presence of either one or both of the studied antibodies (anti-C1q Ab or anti-dsDNA). None of the patients of group 1 had anti-C1q Ab only, and none was negative for anti-C1q Ab and anti-dsDNA Ab together. Levels of anti-C1q Ab and anti-dsDNA Ab were significantly higher in more active LN than less active LN. Anti-dsDNA and anti-C1q antibodies sensitivity and specificity for detection of more active LN was 85.0% and 64.0% and 70.0% and 55.0%, respectively, and 75.0% and 91.0% for both. Both antibodies had a positive correlation with SLEDAI score and proteinuria and a negative correlation with C3 reduction. A high significant positive correlation was detected between anti-C1q Ab and anti-dsDNA Ab.

Conclusion: Anti-C1q Ab, in combination with anti-dsDNA Ab may serve as potential reliable and none invasive markers of SLE disease activity and renal involvement to avoid unnecessary renal biopsies.

1. Introduction

Glomerulonephritis is one of the commonest and most serious manifestations of (SLE). Renal involvement in SLE carries significant morbidity and mortality [1]. Early diagnosis and rapid treatment of lupus nephritis are crucial to improve survival in SLE patients [2].

The complement system plays an important role in the onset as well as throughout the course of SLE. The disease is most often associated with autoantibodies against C1q (anti-C1q), the first component of the classical pathway of complement [3].

A major pathogenic hypothesis is that SLE involves defective renal clearance of immune complexes, and consumption of the early components of the classical complement pathway, such as C1q, C3, and C4, which are strongly associated with the development of active SLE [4]. A Low C1q level is related to the presence of anti-C1q-antibodies with the formation of C1q/anti-C1q immune complexes with subsequent development of glomerulonephritis [5]. Anti-C1q antibodies are present in 20–44% of patients with SLE in cross-sectional studies and are associated with the presence of nephritis [1].

This study was done to assess the role of anti-C1q Ab in combination with anti-dsDNA Ab in detection of SLE disease activity and renal involvement (lupus nephritis).

2. Patients and methods

2.1. Study subjects and design

The current study was observational cross sectional study. Sample was estimated to be 60 adults SLE patients (53 females and 7 males) by using total number of patient available in 1 year 150 cases and the expected percentage of positive C1q Ab in lupus nephritis 50% and the power of our study was 80% with confidence interval 95%. Sample was collected by systematic random method. The study was done in the period from September 2009 to September 2010. Patients ages ranged from 21 and 49 years of mean ± SD (38.1 ± 7.8), disease duration ranged between 2.5 and 4 years of mean ± SD/months (36.4 ± 10.4). Twenty-five (22 females and 3 males) apparently healthy volunteers (from those attending the hospital for donation of blood) were included as controls, they were age and sex matched with the patients, their ages mean ± SD/years were (37.7 ± 8.8).

SLE patients fulfilled at least four criteria of SLE according to American College of Rheumatology [6]. SLE disease activity was based on the SLEDAI score amended in 2000 [7], patients with a score $\leqslant 4$ were considered inactive while those with a score >4 were considered active.

The Systemic Lupus International Collaborating Clinics (SLICC) Damage Index, which has been endorsed by the American College of Rheumatology, was also used [8].

All patients were collected from Rheumatology and Rehabilitation and Internal Medicine Departments in Zagazig University Hospitals, Sharkia governorate, Egypt which is the only hospital in Sharkia governorate that had a specific internal medicine nephrology department that deals with renal biopsy for diagnosis and management of lupus nephritis.

Thirty-two out of the 59 patients were diagnosed as lupus nephritis according to ACR criteria: proteinuria $\geqslant 500$ mg/day and/or red cell casts [6]. The diagnosis of renal involvement was confirmed in 31 of them by renal biopsy as one patient refused to do biopsy, so excluded from the study.

According to renal involvement (LN) and SLEDAI score, patients were divided into four groups: group 1, 11 patients had active disease with LN; group 2, 20 patients had inactive disease with LN; group3, six patients had active disease without LN; group 4, 22 patients had inactive disease without LN.

The biopsies classified according to The International Society of Nephrology/Renal Pathology Society, classes III and IV are considered more active, while classes I, II, and V are considered less active [9]. Five patients were in class II. The majority of patients were in classes III and IV (12 and 8 patients, respectively); six patients were in class V. None of the 31 patients was in class I.

Lupus treatment, at the time of serum sampling, involved low-dose prednisolone (<0.5 mg/kg/day) in thirty patients, high-dose prednisolone ($\geqslant 0.5$ mg/kg/day) in 28 patients, intermittent intravenous cyclophosphamide in nineteen patients, oral azathioprine in 45 patients.

Patients were excluded from the study if they had virus C hepatitis or HIV infection.

Ethical consideration: A written consent was taken from all of the participants after explaining details, benefits as well as risks to them. Only one of LN patients refused to do renal biopsy and so was not included in the study.

2.2. Laboratory procedures

All serum samples were collected in the morning after 9 h fasting. Laboratory investigations were done for all subjects including:

- Complete blood count (CBC), Erythrocyte sedimentation rate (ESR), urine analysis: to detect proteinuria, microscopic examination for pus cells, red blood cells, and casts as indications of renal affection quantitative 24 h urinary protein excretion (turbidity assay).
- Complement C-3 by cobas integra 400 (turbidimetric assay).
- Antinuclear antibody (ANA) was done with the indirect immunoflorescence technique using (Hep-2 substrate, IMMCO Diagnostics, Inc., USA.
- Anti-dsDNA Ab were also determined by EIA (the Binding Site, Birmingham, UK). Positive findings for anti-dsDNA Ab were defined at levels >30 IU/ml.
- IgG anti-C1q antibodies were measured in serum using a commercially available enzyme-linked immunosorbent assay kit (Bühlmann Laboratories, Schönenbuch, Switzerland). In this assay, undigested purified human C1q served as antigen, and sera were diluted and incubated in a high-salt buffer (1 M NaCl) in order to prevent the binding of immune complexes. In the last step, after adding the enzyme substrate tetramethylbenzidine (TMB) to the wells. The reaction is terminated by the addition of stop solution. The optical densities were measured at 450 nm converted into units (U/ml) by being plotted against the autoantibody concentration of the standards given by the manufacturer. To define our cut-off levels of abnormal result, Anti-C1q Ab was measured in 25 healthy controls. Based on these investigations, we calculated an optimized cutoff value at the 98th percentile (that is, 30 U/ml).

Statistics: The collected data were statistically analyzed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA), comparison between group means was done using the Mann–Whitney *U* test while chi-squared test and fisher exact tests were used for qualitative data. For correlation analysis, Spearman's correlation coefficient was used. Odd's ratio and confidence interval were also calculated. The significance level was considered at P value <0.05.

3. Results

3.1. Comparison between SLE patients according to the presence and absence of lupus nephritis

The only significant difference was detected comparing the selected laboratory data of patients groups versus the control group (Table 1).

3.2. Comparison between SLE patients as regard SLEDAI

SLEDAI recorded significantly higher scores in active than inactive patients. Also there was significant difference in levels of anti-C1q Ab, anti-dsDNA Ab, and C3 reduction in active than in inactive patients (Table 2).

3.3. Comparing groups 1 versus 2 regarding anti-C1q Ab and anti-dsDNA Ab

Fig. 1 shows significant elevation of anti-C1q Ab and anti-dsDNA Ab serum levels in group 1 (LN with active SLE) than group 2 (LN with inactive SLE).

Table 1 Demographic, clinical and laboratory data of SLE patients according lupus nephritis, irrespective to SLEDAI.

	SLE with LN (No. = 31)	SLE without LN (No. = 28)
Sex		
Female n.%	27 (87%)	25 (89%)
Male n.%	4 (13%)	3 (11%)
Age/years (mean ± SD)	38.0 ± 7.2	39.0 ± 6.2
Anti-C1q Ab (U/ml)	151.6 ± 14.12*	146.3 ± 15.7
Anti-dsDNA (U/ml)	293 ± 51*	280 ± 69
C3 (g/l)	0.37 ± 0.2*	0.39 ± 0. 3

* Significant when comparing SLE with LN versus without LN.

Table 2 Clinical and laboratory parameters in SLE patients according to SLEDAI, irrespective to renal affection.

	Active SLE (n = 17)	Inactive SLE (n = 42)
Anti-C1q-Ab (U/ml)	141.26 ± 54.22*	66.3 ± 13.22
Anti-dsDNA (U/ml)	285 ± 20*	65 ± 15
C3 (g/l)	0.47 ± 0.13*	0.67 ± 0.14
SLEDAI	10.26 ± 3.11*	3.01 ± 1.0

* Significant difference comparing active versus inactive SLE patients.

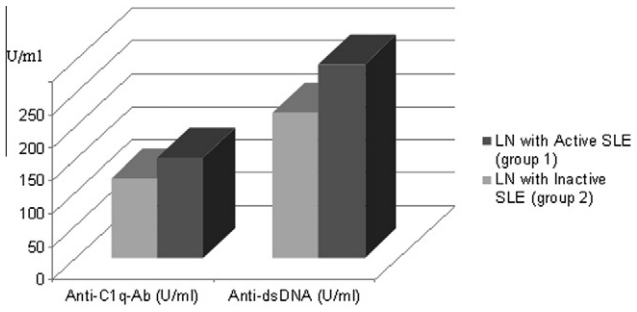

Figure 1 Comparing group 1 versus 2 regarding anti-C1q Ab and anti-dsDNA Ab.

3.4. Comparison between SLE patients regarding the studied antibodies

Presence of anti-C1q Ab, anti-dsDNA Ab, and both of them was significantly associated with LN in active patients. None of group1 patients had anti-C1q Ab only, and none was negative for both anti-dsDNA Ab and anti-C1q Ab (Table 3).

3.5. Comparison between levels of studied antibodies as regard renal biopsy grades

Regarding renal biopsy grades, anti-C1q Ab as well as anti-dsDNA Ab levels were significantly higher in more active LN (biopsy grades III and IV together) than less active LN (biopsy grades II and V together) $P < 0.05$ (Fig 2).

3.6. Significant predictors of studied antibodies

For detection of more active lupus nephritis among the biopsy proven LN patients, sensitivity and specificity for anti-dsDNA Ab was 85.0% and 64.0%, for anti-C1q Ab was 70.0% and 55.0%, and 75.0% and 91.0% for both antibodies. Detection of both anti-C1q Ab and anti-dsDNA Ab could predict 94% of those more active LN and exclude 67% of those who had lower activity of LN proven by biopsy (Table 4).

3.7. Correlation between anti-C1q-Ab and different laboratory and clinical parameters

Serum levels of anti-C1q Ab and anti-dsDNA Ab showed a significant positive correlation with SLEDAI, proteinuria. High significant correlation was found between anti-C1q Ab and anti-dsDNA Ab ($P < 0.001$), they had significant negative correlations with C3 levels ($P < 0.05$) (Table 5).

4. Discussion

Renal involvement is one of the main determinants of poor prognosis of SLE [10]. Kidney biopsy is the golden standard diagnostic tool for the assessment of renal involvement in SLE, however it is invasive procedure and accompanied by potential risks moreover, serial evaluations are sometimes needed but cannot routinely be performed due to the invasive nature [11]. Thus defining an early and reliable and non invasive biomarker of kidney involvement in SLE is highly desirable [12].

Patients with LN irrespective to SLEDAI in the present study showed non significant differences from those without LN regarding serum levels of anti-C1q Ab, anti-dsDNA Ab as well as complement reduction, this data was in agreement with another two studies [13–15].

In the present study, the increase in SLEDAI scores, anti-C1q Ab, anti-ds DNA Ab as well as the reduction of C3 levels was more significant in active patients than inactive patients irrespective of renal affection. Similar to our findings, three other studies found significantly higher titers of anti-C1qAb in patients with active disease compared with those with inactive SLE [14,16,17], also Bernstein et al. [18] reported significantly higher serum levels of anti-dsDNA Ab in the active than in the inactive SLE patients.

We found significant associations and higher titers of anti-C1q Ab, as well as anti-dsDNA Ab when comparing group 1 versus 2, also a significant high detection of these antibodies in patients of group 1 comparing it with groups 3 and 4; that support the indirect role for these antibodies in the pathogenesis of lupus nephritis. Moroni et al. detected a significant asso-

Table 3 Comparison between group 1 versus group 2 as well as other patients groups (3&4) regarding the studied antibodies.

	+ve LN patients (No. = 31)			−ve LN (No. = 28)	OR (CI)
	Active SLE (No. = 11) group 1	Inactive SLE (No. = 20) group 2	OR (CI)	Groups 3 and 4	
Anti-dsDNA Ab +ve ($n = 37$)	11 (100%)*,+	10 (50%)	8.36 (1.13–77.4)	16 (57%)	6.95 (1.06–57.8)
Anti-C1q Ab +ve ($n = 31$)	9 (82%)*,+	10 (50%)	10.5 (1.38–100.7)	12 (42%)	9.5 (1.4–80.9)
Anti-C1q Ab +ve and anti-dsDNA +ve ($n = 24$)	9 (82%)*,+	7 (35%)	8.0 (1.19–62.5)	8 (30%)	6.67 (1.15–43.5)
Anti-C1q Ab +ve and anti-dsDNA −ve ($n = 8$)	0 (0.00%)*,+	4 (19%)	0.0 (0.0–0.2)	4 (13%)	0.0 (0.0–2.34)
Anti-C1q Ab −ve and anti-dsDNA +ve ($n = 14$)	3 (27.30%)	5 (27.0%)	0.7 (0.1–4.46)	6 (20%)	1.13 (0.17–6.8)
Anti-C1q Ab −ve and anti-dsDNA −ve ($n = 17$)	0 (0.00%)*,+	7 (37.0%)	0.0 (0.0–1.2)	10 (37%)	0.0 (0.0–3.0)

+ve, positive or present; −ve, negative or absent.
* Significant when comparing group 1 or 2 versus groups 3 and 4.
+ Significant when comparing group 1 versus 2.

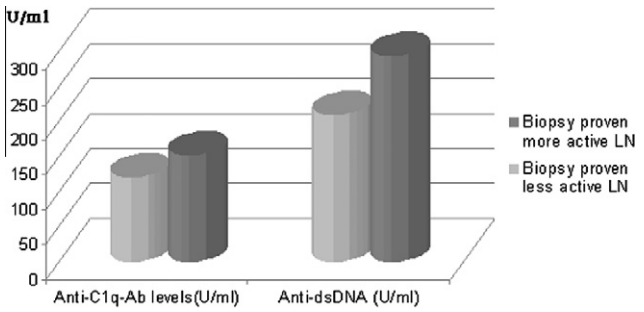

Figure 2 Comparison between levels of studied antibodies as regard renal biopsy grades.

ciation and higher titer of anti-C1q Ab and anti-ds-DNA Ab in active SLE-patients with nephritis [19], And Matrat et al. confirmed that: the presence of anti-C1q and anti-dsDNA aAbs was associated with a high risk of renal flare, whereas the absence of both Abs excluded such an event [20].

Evidence from another study found higher titers of anti-C1q in patients with lupus nephritis also they detected C1q deposition in the kidney tissue [21]. This observation was explained by inhibition of removal of apoptotic cells secondary to complement deficiency induced by these antibodies; they block the clearance of C1q-containing immune complexes, allowing them to deposit in the glomeruli, or they activate the complement cascade and consequently the inflammatory process [22].

None of the patients with LN and active SLE (group1) in the current study had anti-C1q Ab only, and none was negative for both anti-dsDNA Ab and anti-C1q Ab, which is in agreement with another study which reported that anti-C1q antibodies were found in 100% of patients with lupus nephritis and anti-dsDNA antibodies were found in 93.3% of those patients [5].

There is a general agreement in different literatures that the more active classes of biopsy proven LN are classes III and IV, while other classes, namely classes I, II, V, and VI are considered less active that needs limited immunosuppressive therapy [23]. In the present study, anti-C1q Ab as well as anti-dsDNA Ab levels were significantly higher in more active LN (biopsy grades III and IV together) than less active LN (biopsy grades II and V together). This goes hand in hand with study done by Fang et al. who found strong positive association between anti-C1q and the detection of proliferative lupus nephritis [24].

In the current study, for detection of more active LN among the biopsy proven LN patients, sensitivity and specificity for anti-dsDNA Ab was 85.0% and 64.0%, for anti-C1q Ab was 70.0% and 55.0%, and 75.0% and 91.0% for both antibodies. Detection of both anti-C1q Ab and anti-dsDNA Ab could predict 94% of those more active LN and exclude 67% of those who had lower activity of LN proven by biopsy. Trendelenburg et al. reported that, for the detection of an active glomerulonephritis in SLE patients, the anti-C1q assay showed a particularly high sensitivity (97.2%) while specificity was 70.3%. [3].

Concurrent with two other studies [22,25], serum levels of anti-C1q Ab and anti-dsDNA Ab in our study showed a significant positive correlation with SLEDAI scores and proteinuria while they had a significant negative correlation with C3 levels and a significant correlation was found between anti-C1q Ab and anti-dsDNA Ab. These suggested that the detection of anti-C1q antibodies is a potential reliable marker for disease activity, particularly in the renal site [25].

In conclusion, Anti-C1q-antibodies in combination with anti-dsDNA-antibodies have high specificity and sensitivity in detection of SLE disease activity and renal involvement. So together, they may serve as potential reliable and none invasive markers to avoid unnecessary renal biopsies. Both antibodies are recommended to be assessed for follow up and monitoring of LN and SLE activity.

Scope of the article

Renal involvement is one of the main determinants of poor prognosis of systemic lupus erythematosus (SLE). Kidney biopsy is an invasive procedure and accompanied by potential

Table 4 Sensitivity, specificity for studied antibodies among the LN patients.

Auto antibodies	More active LN (No. = 20)	Less active LN (No. = 11)	Sens. (%)	Spec. (%)	+ve predictive value (%)	−ve predictive value (%)
Anti dsDNA (n = 21)	17	4	85	64	81	70
Anti-C1q Ab (n = 19)	14	5	70	55	74	50
+ve (Anti dsDNA and C1qAb) (n = 16)	15	1	75	91	94	67

More active LN, biopsy grades III and IV; Less active LN, biopsy grades II and V).
Sens., sensitivity; Spec., specificity; +ve: positive or present; −ve, negative or absent.

Table 5 Correlation between anti-C1q-Ab and different laboratory and clinical parameters.

	Anti-C1q Ab	Anti-dsDNA Ab	C3	SLEDAI	Proteinuria
Anti-C1q Ab	–	0.69*	−0.32*	0.26*	0.25*
Anti-dsDNA Ab	0.69*	–	−0.58*	0.24*	0.24*

* Significant when $P < 0.05$.

risks. So, the aim of the current study was assessment of the role of anti-C1q Ab in combination with anti-dsDNA Ab in detection of SLE disease activity and renal involvement (lupus nephritis) and we found they may serve as potential reliable and none invasive markers to avoid unnecessary renal biopsies.

Conflicts of Interest

None declared.

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