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THE EFFICIENCY OF ANTI C1Q ANTIBODY AS A DIAGNOSTIC TOOL IN SLE PATIENTS WITH PROLIFERATIVE LUPUS NEPHRITIS

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ABSTRACT

Objective: In this study our main goal is to evaluate the efficiency of Anti C1q antibody as a diagnostic tool in SLE patients with proliferative lupus nephritis. **Method:** This cross-sectional analytic study was conduct at Departments of Nephrology and Rheumatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladeshfrom July 2014 to June 2016. 72 patients were recruited for this study of which the case group was consisted of 36 patients. The rest 36 patients were in the control group. **Results:** During the study, blood pressure was significantly higher among cases than controls. Mild anaemia in case and control groups were found in 15 (41.7%) and 17 (47.2%) patients respectively. Moderate anaemia was present within case and control groups in 13 (36.1%) and 11 (30.6%) patients respectively. The difference in case and control group regarding anaemia was not statistically significant (p=0.962). Level of anti C1q antibody was significantly higher in patients with low serum C4. Similarly, anti C1q antibody level was higher in patients with low serum C3 and positive anti-ds DNA. anti C1q-antibody level was significantly higher in case than that of control. The mean Anti C1q-antibody in case and control group were 37.04 ± 30.01 ng/ml and 4.76 ± 9.16 ng/ml with the range of 1.09 – 123.00 ng/ml and 0.04 – 40.04 ng/ml with the p value of less than 0.001. **Conclusion:** We can conclude that, anti-C1q antibody along with other biomarkers of lupus nephritis (anti dsDNA, C3 and C4) greatly improves the diagnosis of active lupus nephritis in patients with SLE.

KEYWORDS: Anti C1q antibody, systemic lupus erythematosus (SLE), autoimmune disease.

INTRODUCTION

Systemic lupus erythematosus is the prototypic systemic autoimmune disease characterized by heterogeneous, multisystem involvement and the production of an array of autoantibodies. Clinical features in individual patients can be quite variable, ranging from mild joint and skin involvement to severe, life-threatening internal organ disease. Lupus might be confined to the skin, without the presence of systemic involvement.[1]

Anti-complement 1q (anti-C1q) antibodies react with determinants on the collagen-like region of C1q and are measured by ELISA using purified C1q as antigen. In 1984 antibodies directed to C1q (anti-C1q) were reported in the serum of patient with SLE, with a prevalence ranging from 34% to 47%.[2-4] In these patients they strongly correlate with hypocomplementemia and renal flares suggesting that anti-C1q might play a pathogenic role.[5]

Whereas most of the clinical studies have shown a high negative predictive value of anti-C1q for the occurrence of a severe lupus nephritis ranging up to 100%.[6]

In this study our main goal is to evaluate the efficiency of Anti C1q antibody as a diagnostic tool in SLE patients with proliferative lupus nephritis.

Objective

General objective

- To assess the efficiency of Anti C1q antibody as a diagnostic tool in SLE patients with proliferative lupus nephritis.

Specific objective

- To identify clinical parameters among patients.
- To detect immunological findings among cases.

METHODOLOGY

Study type

It was a cross-sectional analytic study

Study place and period

This study was done in the Departments of Nephrology and Rheumatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladeshfrom July 2014 to June 2016.

Study Population

Adult patients diagnosed as a case of SLE with active urinary sediment undergone renal biopsy for suspected proliferative lupus nephritis were selected for the study. 72 patients were recruited for this study of which the case group was consisted of 36 patients. The rest 36 patients were in the control group.

Sampling technique

Purposive sampling was done.

Study Procedure

During the written informed consents were taken from all patients. After taking informed consent the following data were collected from each patient: the findings of history and clinical examination. Subjects were selected on the basis of inclusion criteria.All case group undergoing renal biopsy to find out the histopathological disease activity.

Data analysis

Computer based statistical analysis were carried out with appropriate techniques and systems. All data were recorded systematically in preformed data collection form. Quantitative data were expressed as mean and standard deviation and qualitative data were expressed as frequency distribution and percentage. Statistical analyses were performed by using window-based computer software with Statistical Packages for Social Sciences (SPSS-21) (SPSS Inc, Chicago, IL, USA). Association between categorical variables was done by chi-square test and continuous variable by t-test and Mann-Whitney U test. For all statistical tests, we considered p value <0.05 as statistically significant.

RESULTS

In table 1 shows age distribution of the patients. Maximum (50.0%) patients were in the age group of 21 – 30 years among cases and mean age was 24.55 ± 6.32 years in case group. Similarly, maximum (55.6%) patients were in age group 21 – 30 years and mean age was 24.63 ± 6.32 years in the control group. The following table is given below in detail:

Table 1: Distribution of patients according to age (n=72).

Age (years)	Group		p value
	Case n (%)	Control n (%)	
18 – 20	13 (36.1)	10 (27.8)	
21 – 30	18 (50.0)	20 (55.6)	
>30	5 (13.9)	6 (16.7)	
Total	**36 (100.0)**	**36 (100.0)**	
Mean ± SD	24.55 ± 6.32	24.63 ± 6.32	0.956
Range	18 – 45	18 – 44	

Unpaired t test was done to measure the level of significance. In figure-1 shows gender distribution of the patients where females were predominant to males in both groups. In case and control groups females were 32 (88.9%) and 33 (91.7%) respectively. In case and control groups males were 4 (11.1%) and 3 (8.3%) respectively. Female to male ratio was 8:1 among cases and 11:1 among controls. The difference in case and control group regarding gender distribution was not statistically significant (p=0.691). The following figure is given below in detail:

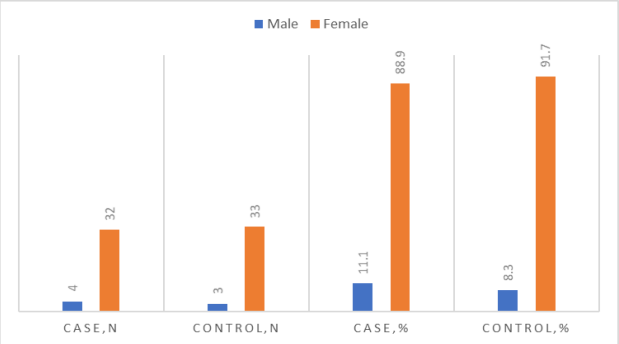

Figure-1: Gender distribution of the patients.

In table-2 shows frequency of the different clinical presentations of the patients in both groups. Mild anaemia in case and control groups were found in 15 (41.7%) and 17 (47.2%) patients respectively. Moderate anaemia was present within case and control groups in 13 (36.1%) and 11 (30.6%) patients respectively. The difference in case and control group regarding anaemia was not statistically significant (p=0.962). Among cases, mild and moderate edema were present in 25 (69.4%) and 9 (25.0%) cases respectively. Malar rash, Discoid rash, Photosensitivity, Oral ulcers, Arthitis, Serositis, Neurological disorder, Hematologic disorder, Immunologic disorder, were examined and it was found that their frequency were statistically non significantly

different between the two groups. The following table is given below in detail:

Table-2: Frequency of clinical parameters among patients (n=72).

History/Examination	Group		P value
	Case n (%)	Control n (%)	
Anemia			
Mild	15 (41.7)	17 (47.2)	0.962[#]
Moderate	13 (36.1)	11 (30.6)	
Severe	2 (5.6)	2 (5.6)	
ACR criteria for SLE			
Malar rash	28 (77.8)	24 (66.7)	0.293[#]
Discoid rash	7 (19.4)	5 (13.9)	0.527[#]
Photosensitivity	26 (72.2)	23 (63.9)	0.617[#]
Oral ulcers	31 (86.1)	27 (75.0)	0.234[#]
Arthitis	32 (88.9)	28 (77.8)	0.206[#]
Serositis	11 (30.6)	9 (25.0)	0.599[#]
Renal disorder	36 (100)		
Neurological disorder	8 (22.2)	6 (16.7)	0.551[#]
Hematologic disorder	11 (30.6)	9 (25.0)	0.599[#]
Immunologic disorder	27 (75.0)	25 (69.4)	0.599[#]
Antinuclear antibody	36 (100.0)	32 (88.9)	0.040[#]
Blood pressure	Mean ± SD	Mean ± SD	
Systolic BP (mmHg)	132 ± 14	120 ± 6	0.001[##]
Diastolic BP (mmHg)	86 ± 9	79 ± 2	0.001[##]

[#]Chi-square test was done to measure the level of significance.
[##]Unpaired t test was done to measure the level of significance.

In table-3 shows anti C1q level among the cases in different immunological findings (eg. Anti-ds DNA, serum C3 and C4) at the time of renal biopsy. Level of anti C1q antibody was significantly higher in patients with low serum C4. Similarly anti C1q antibody level was higher in patients with low serum C3 and positive anti-ds DNA. Anti-ds DNA was positive in 16 (44.4%) in which the mean ofAnti C1q antibodywas41.28 ± 30.86 ng/ml (p=0.093). Low serum C3 was 27 (75.0%) cases and the mean Anti C1q antibody was 41.96 ± 30.19 ng/ml (p=0.192). Again, low serum C4 was found among 14 (38.9%) patients and the mean Anti C1q antibody was 53.83 ± 29.96 ng/ml (p=0.010). The following table is given below in detail:

Table-3: Immunological findings among cases (n=36).

Lab parameters	n (%)	Anti C1q antibody (mean ± SD)	p value
Anti-ds DNA			
• Positive	16 (44.4)	41.28 ± 30.86	0.093
• Negative	20 (55.6)	24.33 ± 24.56	
• Serum C3			
• Normal	9 (25.0)	22.29 ± 25.54	0.192
• Low	27 (75.0)	41.96 ± 30.19	
• Serum C4			
• Normal	22 (61.1)	26.36 ± 25.26	0.010
• Low	14 (38.9)	53.83 ± 29.96	

Mann-Whitney U test was done to measure the level of significance

In table-4 shows histopathological class of SLE and activity of LN among cases. Highest number of patients presented with Class IV and then in Class III. Most patients had active LN. The following table is given below in detail:

Table-4: Distribution of patients according to histopathological class of SLE (n=36).

Renal biopsy	Active	Active & chronic	Chronic
Class II (3)	3 (13.0)	0 (0.0)	0 (0.0)
Class III (4)	4 (17.4)	0 (0.0)	0 (0.0)
Class IV (26)	14 (60.9)	12 (100.0)	0 (0.0)
Class V (2)	2 (8.7)	0 (0.0)	0 (0.0)
Class VI (1)	0 (0.0)	0 (0.0)	1 (100.0)

In table-5 shows immune deposit in different classes of Lupus Nephritis. In histopathological classification IgG was 26(100.0%) present in Class IV variant. IgM was present in 25(96.1%) patients. Classical 'full house' deposition was present in almost all patients. The following table is given below in detail:

Table-5: Immune deposit in different classes of Lupus Nephritis.

Histopathological classification	IgG n (%)	IgM n (%)	IgA n (%)	C3 n (%)	C1q n (%)
Class II (3)	2 (66.7)	3 (100.0)	1(33.3)	2 (66.7)	0 (0.0)
Class III (4)	4 (100.0)	4 (100.0)	4 (100.0)	3 (75.0)	4 (100.0)
Class IV (26)	26 (100.0)	25 (96.1)	24 (92.3)	26 (100.0)	21 (80.7)
Class V (2)	2 (100.0)	2 (100.0)	1 (50.0)	2 (100.0)	1 (50.0)
Class VI (1)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)

Table-6 shows that anti C1q-antibody level was significantly higher in case than that of control. The mean Anti C1q-antibody in case and control group were 37.04 ± 30.01 ng/ml and 4.76 ± 9.16 ng/ml with the range of 1.09 – 123.00 ng/ml and 0.04 – 40.04 ng/ml with the p value of less than 0.001. The following table is given below in detail:

Table-6: Anti C1q-antibody level in study subjects (n=72).

Anti-C1q antibody (ng/ml)	Mean ± SD	Range (min – max)
Case	37.04 ± 30.01	1.09 – 123.00
Control	4.76 ± 9.16	0.04 – 40.04
p value	< 0.001	

Mann-Whitney U test was done to measure the level of significance. In figure-2 shows ROC curve of anti C1q antibody. Area under curve (AUC) of Anti C1q antibody was 0.887 (95%CI 0.865 – 0.905). The following figure is given below in detail:

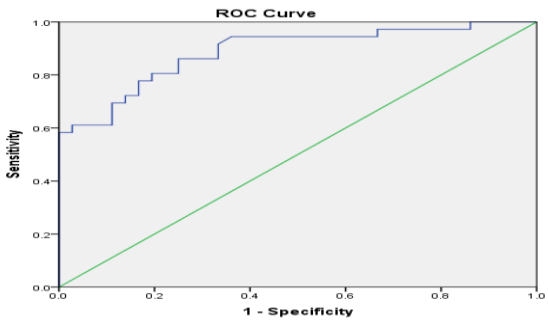

Figure-2: ROC curve of anti C1q antibody.

Figure 3 shows Box plot of Anti C1q antibody level in different lupus nephritis classes. Mean anti C1q antibody level was highest in class III followed by class IV. The following figure is given below in detail:

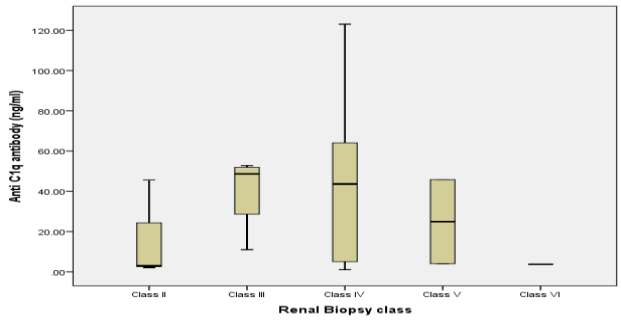

Figure 3: Box plot of Anti C1q antibody level in different lupus nephritis classes.

Figure-4 shows association of Renal activity score with Anti C1q antibody levels. Mean anti-C1q antibody levels were found to be greater in patients with higher renal activity scores. The following figure is given below in detail:

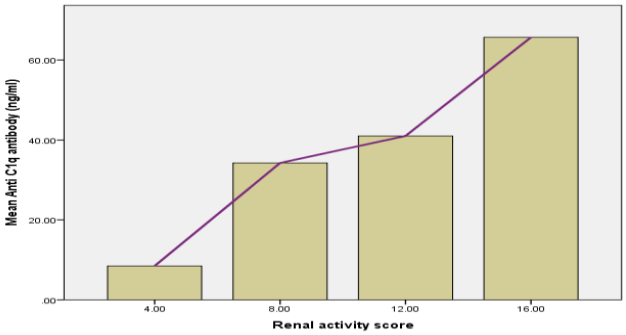

Figure 4: Association of Renal activity score with Anti C1q antibody levels.

DISCUSSION

Mild anaemia in case and control groups were 15 (41.7%) and 17 (47.2%) cases respectively. Moderate anaemia were present in 13 (36.1%) and 11 (30.6%) in case and control groups respectively. Among cases, Mild and moderate edema were present in 25 (69.4%) and 9 (25.0%) cases respectively. Malar rash, discoid rash, photosensitivity, oral ulcers, arthitis, serositis, neurological disorder, hematologic disorder, immunologic disorder, antinuclear antibody were examined and was found that these were statistically not significant. SLE is a chronic autoimmune disease that can affect almost any organ system; thus, its presentation and course are highly variable, ranging from indolent to fulminant. In childhood-onset SLE, there are several clinical symptoms more commonly found than in adults, including malar rash, ulcers/mucocutaneous involvement, renal involvement, proteinuria, urinary cellular casts, seizures, thrombocytopenia, hemolytic anemia, fever, and lymphadenopathy. In adults, Raynaud, pleuritis and sicca are twice as common as in children and adolescents.[7] The classic presentation of a triad of fever, joint pain, and rash in a woman of childbearing age should prompt investigation into the diagnosis of SLE.[8]

Anti C1q-antibody level was significantly higher in case than that of control. The mean Anti C1q-antibody in case and control group were 37.04 ± 30.01 ng/ml and 4.76 ± 9.16 ng/ml with the range of 1.09 – 123.00 ng/ml and 0.04 – 40.04 ng/ml with the p value of less than 0.001.

One study have reported similar result and also have added that the prevalence of anti-C1q antibodies in SLE ranges from about 30% to 60%.[10] The marked variance between the results may be due to the differences between individually prepared assays and commercialELISA kits used to determine the levels of anti-C1q antibodies.[11] In addition, anti-C1q antibodies are closely linked to LN, and the study cohorts might differ as to the prevalence of LN among the patients included. Indeed, anti-C1q antibodies are increasingly being used in the diagnosis of active LN.

In histopathological classification IgG was 26(100.0%) present in Class IV variant. IgM was present in 25(96.1%) patients. Area under curve of Anti C1q antibody was 0.887 (95% CI 0.865 – 0.905). The mean anti C1q antibody level was higher in class III followed by class IV. Mean anti-C1q antibody levels were found to be greater in patients with higher renal activity scores. Another study have raised other possible explanations for the absence of anti-C1q antibodies in some patients with LN and was followed 21 SLE patients with active renal disease and found all patients with proliferative LN to have a high ongoing production of anti-C1q antibodies in peripheral cells although not every patient had positive serum levels.[12] The study in 2002 reported that only 11 of 18 patients with biopsy-verified LN were anti-C1q positive. However, C1q was low in most of these patients and correlated negatively with anti-C1q antibodies, thus implying that the antibodies might bind to C1q and form immune complexes, or they might be sequestered in the kidneys.[7] These findings were supported by one study who suggested measuring both anti-C1q antibodies and C1q antigen in order to predict the presence of LN and assess the activity of SLE.[13]

CONCLUSION

We can conclude that, anti-C1q antibody along with other biomarkers of lupus nephritis (anti dsDNA, C3 and C4) greatly improves the diagnosis of active lupus nephritis in patients with SLE.

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