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Original Article

Internal Medicine Section

Anti-C1q Antibody is Associated with Renal and Cutaneous Manifestations in Asian Indian Patients with Systemic Lupus Erythematosus

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ABSTRACT

Introduction: C1q play an important role in clearance of immune complexes and apoptotic cell debris. Impaired clearance leads to exposure of C1 native antigen and development of anti-C1q antibody formation. Anti-C1q antibody is well studied in Systemic Lupus Erythematosus (SLE). Significance of anti-C1q Ab in Indian SLE patients and their clinical manifestations is not clear.

Aim: The aim of this study was to investigate associations between anti-C1q antibody and clinical as well as serological markers of SLE.

Materials and Methods: Retrospective study of SLE patients fulfilling either American College of Rheumatology (ACR) 1990 or Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification criteria were recruited from inpatients and outpatients services of the Clinical immunology and Rheumatology Department, Christian Medical College at Vellore, India between March 2013 and January 2015. Anti-C1q antibody was assayed by ELISA (Demeditec Diagnostics GmbH, Germany). Logistic regression analysis was performed to find the association of anti-C1q antibodies with serological and clinical parameters in SLE including Lupus Nephritis (LN).

Results: Sixty nine patients (54.76%) out of 126 SLE patients had LN. Anti-C1q levels were higher in patients with LN as compared to those without ($p<0.05$). Anti-C1q antibody was also significantly associated with positive C1q immunofluorescence staining in renal biopsy specimens ($p<0.05$). Overall, renal Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) {OR 1.35 (1.08-1.69)}, low C4 {OR 3.11 (1.04-9.26)} and mucocutaneous manifestation {OR 4.72 (1.38-16.05)} were independently associated with anti-C1q levels in serum.

Conclusion: Renal SLEDAI, low C4 and mucocutaneous manifestations were independently associated with raised anti C1q antibody in SLE patients.

Keywords: Anti nucleosome antibody, Complement C4, Lupus nephritis

INTRODUCTION

SLE is a chronic autoimmune disease characterised by multi organ manifestations. LN has been reported in less than 50% of SLE patients from Asia and this serious complication is associated with substantial morbidity and mortality [1,2].

The initial complement component C1q activates classical complement pathway and plays an important role in the clearance of immune complexes and apoptotic cell debris [1]. C1q specifically binds to early apoptotic cells and initiates complement activation in order to clear dying cells [2,3]. Impaired clearance of apoptotic cells leads to exposure of neo epitopes in collagen like region of C1 which forms the binding site for anti-C1q IgG antibody [2,4]. This binding results in augmentation of complement activation. Anti-C1q antibody is seen in hypocomplementemic urticarial vasculitis syndrome (100%), mixed connective tissue disorder (94%), Felty's syndrome (76%), SLE (30-60%) and Rheumatoid vasculitis (32%) [5]. C1q deficiency-associated SLE/SLE-like disease is known to present commonly with discoid rash and oral ulcers, whereas arthritis is a less common feature in this subset [6].

Anti-C1q antibody is present in approximately one third of patients with SLE, especially in those with high disease activity and renal involvement [7]. Anti-C1q Ab can predict renal flare. Hence, anti-C1q Ab can be used as a biomarker for monitoring patients with LN [8–11]. There are also few reports showing no association between anti-C1q antibodies and LN [12,13]. Currently no clear explanations are known for these discrepant data on clinical associations of anti-C1q antibody. Genetic susceptibility and ethnicity can influence anti-C1q antibody [14,15]. Anti-C1q antibody is also more common in Asians as compared to Caucasians and African Americans. Levels of anti-C1q antibody is reported to be higher in younger SLE patients with age below 35 years [15]. Given the high incidence of LN and younger age of onset in Asian lupus patients, it is likely that our patients have high anti-C1q antibodies [16,17]. The aim of this study, therefore, was to find out any association between anti-C1q antibody and other laboratory markers as well as clinical features in our patients with SLE.

MATERIALS AND METHODS

This retrospective study was carried out using laboratory and electronic records of our SLE patients attending outpatient and inpatient services of the Department of Clinical Immunology and Rheumatology between March 2013 and January 2015. Hospital data of patients fulfilling ACR 1990 or SLICC 2012 classification criteria for SLE who underwent anti-C1q antibody test during this period, were retrieved from laboratory register. Relevant clinical, laboratory and serological parameters corresponding to the time of anti-C1q assay were noted from hospital electronic medical record. Clinical parameters noted included presence of organ system involvement (e.g., arthritis, skin manifestations, serositis, and central nervous system involvement), thromboembolic events, major infections as well as demographic features like disease duration prior to presentation. Laboratory findings from hospital electronic medical records were also noted including ESR, haemoglobin, blood counts, complement C3 and C4, Urine Protein/Urine Creatinine ratio (UP/UC), presence of autoantibodies (like anti-dsDNA, anti nucleosome antibody and antiphospholipid antibodies) and biopsy results. Presence of lupus anticoagulant or anti cardiolipin antibody in our SLE patients was

considered indicative of positive antiphospholipid antibody status. When other laboratory test results were not available at the precise date of anti-C1q antibody assays, test results within 15 days of the anti-C1q antibody measurement were accepted as concurrent test results [18]. Disease activity score was calculated by SLEDAI using the relevant data from the electronic record of the hospital at the time of anti-C1q assay. Accordingly, disease activity in all SLE patients was classified as mild, moderate, or severe, based on their SLEDAI scores (mild <8, moderate 8-18, and severe >18). Renal SLEDAI score was calculated to assess kidney disease activity as described earlier [19].

Blood samples for anti-C1q antibody assay were collected from patients during their hospital visits irrespective of disease duration or dose of immunosuppressants. Anti-C1q Antibody was assayed by commercially available ELISA kit (Demeditec Diagnostics GmbH, Germany). Results were expressed as unit/ml (U/ml) and serum level more than or equal to 10 U/ml (cut off value), was considered positive, as recommended by the manufacturer.

This study was approved by the Institutional Review Board (ethics and research committee) of Christian Medical College, Vellore, Tamil Nadu, India.

STATISTICAL ANALYSIS

Continuous data are presented as mean (SD) or median (range) and categorical data are presented as frequency. Mann-Whitney test was performed to find out any significant difference of anti-C1q Ab titer between: a) Patients with and without LN; and b) between patients with active LN and Inactive LN. To identify any association of clinical and laboratory variables with anti-C1q antibody, univariate logistic regression analysis was done. Organ involvement, major infection and thromboembolic events were categorised as present or absent at the time of anti-C1q antibody assay. Laboratory variables included C3 and C4 levels, ESR and urine protein/urine creatinine ratio, and these were categorised as low or normal whereas anti-dsDNA antibody, anti nucleosome antibody and anti phospholipid antibodies were categorised as positive or negative. The relevant variables with p<0.05 by univariate logistic regression analysis were subjected to multivariable logistic regression analyses. A two tailed p-value of <0.05 was considered as significant. The statistical analysis of data was done using STATA 13.1 (StataCorp LP, Texas, USA) statistical package.

RESULTS

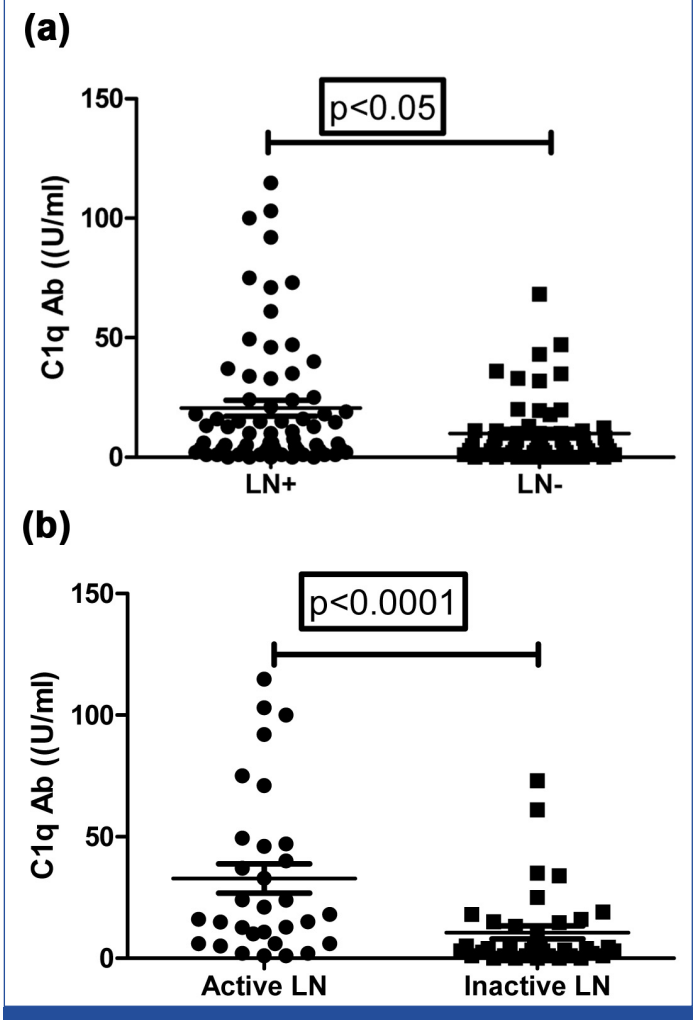
Baseline characteristics of 126 patients included in the study are shown [Table/Fig-1]. LN was present in 54.76% of the patients. Anti-C1q antibody was present in 42.85% of the patients. Anti-C1q levels were significantly higher in patients with LN, as compared to lupus patients without LN (p<0.05) [Table/Fig-2a]. Similarly, anti-C1q levels were significantly higher in patients with active LN, as compared to inactive LN (p<0.05) [Table/Fig-2b].

Association of Anti-C1q Antibody in all SLE Patients

Results of univariate analysis are shown [Table/Fig-3]. Variables found to be significant in univariate analysis were subjected to multivariate logistic regression with the exception of anti nucleosome antibodies and SLEDAI [Table/Fig-3]. Anti nucleosome antibody tests were available only for 91 patients, hence it was excluded from multivariable analysis. SLEDAI was also excluded from multivariate analysis, as it encompasses some of the other clinical and lab variables used in analysis. In multivariate analysis, low C4 (OR 3.11), mucocutaneous features (OR 4.72) and higher renal SLEDAI (OR 1.35) were found to be significantly associated with positive anti-C1q antibody. On removing renal SLEDAI from analysis, UP/UC {OR 1.77(0.63-4.95), (p<0.05)} also attained significance.

Parameters	Total number of patients (n=126)
Age in years - Median(range)	28 (13-62)
Male: Female (%)	11 (8.73%):115 (91.26%)
Lupus nephritis	69 (54.76%)
Serositis	7 (5.6%)
Arthritis	46 (36.5%)
Mucocutaneous manifestation	51 (40.47%)
Neuropsychiatric manifestation	17 (13.5%)
Major Infection	5 (3.9%)
Thromboembolic events	6 (4.7%)
Median disease duration at presentation in months (range)	6 (1-96)
Median serum creatinine	0.72 (0.1-2.21)
Median 24 hour urinary protein (mg)	283 (99.5-949.5)
Nephrotic range proteinuria (n)	6/126 (4.76%)
Impaired renal functions (n)	4/126 (3.17%)
Systemic arterial hypertension (n)	5/126 (3.96%)
Median SLEDAI (range)	6 (0-29)
Mean Renal SLEDAI (range)	1.7 (0-16)
Median C1q Ab titers	6 (0-114.9)
Presence of autoantibodies	**n/N* (%)**
Anti-C1q antibody	54/126 (42.85%)
Anti nucleosome antibody	46/91 (50.54%)
anti-dsDNA antibody	84/125 (67.2%)
anti phospholipid antibodies	30/106 (28.3%)

[Table/Fig-1]: Patients characteristics.
*n represents the number of patients in whom the test results were available.



[Table/Fig-2]: Scatter plot show anti-C1q Ab levels; (a). Between patients with LN (n-69) and without LN (n-57); (b). Between patients with active LN (n-32) and Inactive LN (n-37)
*Mann-Whitney U test was used.

Parameters	Univariate logistic regression analysis		Multivariate logistic regression analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Anti nucleosome Abs	6.57 (2.63-16.43)	0.001*	ND	-ND
Anti-dsDNA	4.1 (1.74-9.64)	0.01*	1.34 (0.44-3.82)	0.629
Antiphospholipid Abs	0.74 (0.31-1.74)	0.493	ND	ND
Low C3	4.5 (2.09-9.68)	0.001*	1.37 (0.44-4.28)	0.581
Low C4	4.95 (2.3-10.67)	0.001*	3.11 (1.04-9.26)	0.05*
ESR	1.69 (0.71-3.99)	0.230	ND	ND
Haemoglobin	0.91 (0.75-1.1)	0.343	ND	ND
Leucopenia	0.966 (0.48-1.94)	0.923	ND	ND
UP/UC	4.43 (2-9.77)	0.001*	1.77 (0.63-4.95)	0.276
Serositis	2.12 (0.56-7.93)	0.262	ND	ND
Arthritis	1.51(0.69-3.3)	0.292	ND	ND
Mucocutaneous	2.65 (1.12-6.31)	0.05*	4.72 (1.38-16.05)	0.05*
SLEDAI-Moderate	6.33 (2.28-17.3)	0.001*	ND	ND
SLEDAI-Severe	17.4 (5.34-56.7)	0.001*	ND	ND
Renal SLEDAI	1.57 (1.29-1.92)	0.001*	1.35 (1.08-1.69)	0.01*

[Table/Fig-3]: Associations of anti- C1q antibodies with clinical manifestations and laboratory parameters in SLE patients including lupus nephritis (univariate analysis and multivariate analysis).
*ND- Not Done.

Parameters	Odds ratio (95% CI)	p-value
Anti nucleosome Abs	10.68 (2.88-39.62)	0.001*
Anti-dsDNA	6.25 (1.79-21.77)	0.005*
Antiphospholipid Abs	0.73 (0.21-2.5)	0.627
C3	8.17 (2.63-25.32)	0.001*
C4	5.01 (1.79-14.05)	0.005*
ESR	3.72 (1.34-10.24)	0.068
Haemoglobin	1.06 (0.82-1.39)	0.621
Leucopenia	0.66 (0.25-1.72)	0.398
UP/UC	3.71 (1.34-10.24)	0.05*
Serositis	1.38 (0.28-6.68)	0.691
Arthritis	2.91 (0.79-6.07)	0.131
Mucocutaneous	1.35 (0.45-4)	0.583
Renal SLEDAI	1.52 (1.2-1.92)	0.001*

[Table/Fig-4]: Associations of anti- C1q antibodies with clinical manifestations and laboratory parameters in SLE patients with LN as revealed by univariate logistic regression.
*Significant at 5% level of significance.

Association of Anti-C1q Antibody in Lupus Nephritis

We also did a separate univariate analysis with laboratory markers and clinical features in LN patients (n-69) [Table/Fig-4]. Anti-nucleosome antibody, anti-dsDNA antibody, low C3 and low C4, high UP/UC and renal SLEDAI were found to be significantly associated with anti-C1q antibody. No significant association was found when these parameters underwent multivariate logistic regression.

DISCUSSION

Anti-C1q antibody is associated with SLE, in particular with LN. The result of present study on associations of anti-C1q antibody with LN in Asian Indian population is consistent with previous studies reported in western as well as Asian population. Multivariate analysis didn't reveal any significant association of anti-C1q antibody in LN. In the whole SLE cohort, however, low C4, mucocutaneous and renal SLEDAI were independently associated with elevated serum anti-C1q antibody levels.

The frequency of anti-C1q antibodies in all SLE patients and LN subgroup were 42.3% and 50.7%, respectively in the present study as compared to 58.3% and 60%, respectively in a study from Western India [20]. The difference in frequencies could be accounted by larger sample size in our study. The prevalence of anti-C1q in another study consisting of multiethnic SLE patients was 28%, which is lower than the present study. In our study, anti-C1q antibody levels were significantly higher in patients with LN as compared to lupus patients without LN ($p<0.05$), which has not been reported previously [20–22]. Association of anti-C1q Ab with anti nucleosome Ab, anti-dsDNA Ab and urine protein/creatinine ratio in LN patients was not established in our multivariate analysis, possibly due to relatively lesser number of subjects with LN. Our finding of a pronounced association of anti-C1q antibody with anti nucleosome antibody and also a fairly strong association with anti dsDNA antibody may be explained by plausible biological basis. Nucleosome enhances binding of C1q in glomerular endothelial cells undergoing apoptosis and this interaction leads to potential binding of anti-C1q autoantibodies [23]. Anti-C1q antibody is considered to be predictor of active LN and in our study too, we found higher levels in active disease, as compared to inactive LN, similar to observation by others [24,25]. However, some reports also suggest that SLE patients negative for anti-C1q antibody are unlikely to get LN [10,26].

Association of renal SLEDAI with anti-C1q antibody observed in our study confirms utility of this antibody as a biomarker for renal involvement in SLE [15]. In the multivariate analysis, once renal SLEDAI was eliminated, UP/UC ratio {OR 1.77(0.63-4.95)} was also a significant association of anti-C1q antibody. This may imply that UP/UC levels are an important contributing factor towards renal SLEDAI in lupus nephritis patients with high levels of anti-C1q antibodies. This is again consistent with previous findings showing association of anti-C1q antibody with proteinuria and renal disease activity [8,27]. Further, combination of anti-C1q antibody and anti-dsDNA antibody predicts poorer renal outcome indicating active renal disease [28]. Results from this study also may suggest that anti-C1q antibody in combination with anti nucleosome antibody can be a better reflector of active LN.

In our SLE cohort, anti-C1q antibody is also highly associated with mucocutaneous involvement {OR 4.72 (1.38-16.05)}. Data on association of cutaneous features with anti-C1q antibody is scarce in SLE literature [29]. Bălănescu E et al., reported that SLE patients had increased titers of anti-C1q in serum [30]. Anti-C1q antibodies decrease complement proteins in circulation including C1q [31]. Congenital deficiency of C1q have been observed in early onset photosensitive SLE [32]. Although, low C1q in adult SLE patients is an acquired phenomenon caused by anti-C1q antibodies, could this have produced cutaneous manifestations as in patients with congenital C1q deficiency?

Nevertheless, association of early onset SLE with deficiency of C1q is well known [33]. In our study also, anti-C1q antibody levels were different between age groups with a cut off of 35 years of age; although this did not reach statistical significance, the trend was visible ($p=0.055$). Orbai AM et al., found that anti-C1q antibody level was higher in SLE patients with age below this age cut off [15]. These data support the notion that anti-C1q antibodies were more common in younger onset SLE patients.

LIMITATION

Limitation of this study includes retrospective design and smaller sample size.

CONCLUSION

In conclusion, low complement protein C4, mucocutaneous features and higher renal SLEDAI were independently associated with high anti-C1q antibody titre. Anti-C1q antibody, therefore, may act as a surrogate marker of renal and cutaneous involvement in SLE.

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