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Evolving phenotype of systemic lupus erythematosus patients and it's correlation with antibody against c1q

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Abstract---Backgrounds: Autoantibodies against C1q are strongly linked to immune-complex disorders like systemic lupus erythematosus (SLE). Although anti-C1q antibodies have received much interest in the recent years, their biological functions remain unclear. Aim and objectives: The main aim of this study was to analyze the phenotype of systemic lupus erythematosus at first presentation and during follow-up at Qena university hospital. Subjects and methods: This cross-sectional study was conducted at Qena university hospital. The study was conducted on 100 systemic lupus erythematosus patients. Results: Regarding the relation between lupus activity and anti-C1q antibody we found that there were highly statistically significant differences between lupus activity groups according to anti-C1q antibody. We also found that there were highly statistically significant differences between lupus activity groups according to anti-C1q with highly increasing in anti-C1q in

patients with lupus activity when comparing with patients without lupus activity. Conclusion: Anti-C1q antibodies were strongly associated with lupus disease activity in SLE patients, suggesting that it may be a reliable, sensitive and non-invasive serological marker for identification of SLE patients with active SLE disease.

Keywords---Anti-C1q, systemic lupus erythematous, lupus nephritis, complement, proteinuria.

Introduction

SLE is a chronic disease that causes inflammation in connective tissues, such as cartilage and the lining of blood vessels, which provide strength and flexibility to structures throughout the body. The signs and symptoms of SLE vary among affected individuals, and can involve many organs and systems (Scolnik et al., 2014). SLE is one of a large group of conditions called autoimmune disorders that occur when the immune system attacks the body's own tissues and organs (Pons-Estel et al., 2010). Affected individuals may also have alopecia, ulcerations in mucosae of the mouth, nose, or, less commonly, the genitals (Ahmadpoor et al., 2014). The exact prevalence is difficult to determine because many of the signs and symptoms of SLE resemble those of other disorders. Diagnosis may be delayed for years, and the condition may never be diagnosed in some affected individuals. Females develop SLE about nine times more often than males. It is most common in younger women, peaking during the childbearing years; however, 20 percent of SLE cases occur in people over age 50 (Petri et al., 2012). Complement C1q is a cationic glycoprotein produced by immune cells which is the first component identified in the canonical pathway of complement activation. It's noticed that it is elevated in some autoimmune diseases mostly urtacarial Vasculitis.

Patients and Methods

This study was a cross-sectional study

Study Setting

assess and describe the phenotype of systemic lupus and assess the correlation with antibody against c1q.

Study subjects

A total of 100 patients attending to University Hospitals of Qena known to be lupus according 2019 European League against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus and record which type of lupus start and each continue and measure the level of antibody against c1q in each case. All of the participants had been subjected to the following: Full history (demographic data and personal history, detailed history of general health condition and chronic or current diseases), general examination including vital signs, systematic examinations of the 4 systems

researched (CVS, neuropsychiatric, renal, blood), investigations: investigations of SLE patients (routine ,immunological profile , renal biopsy in lupus nephritis) and assessment of disease activity by SLEDAI (systemic lupus disease activity index). Positivity and negativity of antibody against c1q, to measure its titre and to asses its correlation with lupus activity.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0**. (**Armonk, NY: IBM Corp**),** Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean and standard deviation. Significance of the obtained results was judged at the 5% level.

Results

Table 1
Distribution of studied sample according to demographic data

	Number	Percent
Age (years)		
Range	29 – 45	
Mean±S.D.	37.50±5.134	
Sex		
Male	38	38.0
Female	62	62.0

Table (1) shows demographic data of the studied group. Age was ranged between 29 – 45 years with mean value 37.50±5.134 years. Male cases were 38(38.0%) while female cases were 62(62.0%).

Table 2
Distribution of studied sample according to Disease duration and SLEDAI score

	Min. – Max.	Mean±S.D.
Disease duration	2.8 – 6.8	4.40±0.987
SLEDAI score	0 – 24	5.62±8.114

Disease duration was ranged between 2.8 – 6.8 years with a mean value of 4.40±0.987 years. SLEDAI score was ranged between 0 – 24 with a mean value of 5.62±8.114. Table (2)

Table 3
Distribution of studied sample according to ACL antibody

ACL antibody	Number	Percent
Negative	85	85.0
Positive	15	15.0

Total	100	100

ACL antibody distribution of the studied group and it show that 15(15.0%) had ACL antibody. Table (3)

Table 4
Distribution of studied sample according to Anti-C1q antibody

Anti-C1q antibody	Number	Percent
Negative	80	80.0
Positive	20	20.0
Total	100	100

Anti-C1q antibody distribution of the studied group and it show that 20(20.0%) had Anti-C1q antibody. Table (4)

Table 5
Distribution of studied sample according to Anti-ds DNA antibody

Anti-ds DNA antibody	Number	Percent
Negative	84	84.0
Positive	16	16.0
Total	100	100

Anti-ds DNA antibody distribution of the studied group and it show that 16(16.0%) had Anti-ds DNA antibody. Table (5)

Table 6
Distribution of studied sample according to ANA antibody

ANA antibody	Number	Percent
Negative	69	69.0
Positive	31	31.0
Total	100	100

ANA antibody distribution of the studied group and it show that 31(31.0%) had ANA antibody. Table (6)

Table 7
Distribution of studied sample according to Anti-ribosomal P antibody

Anti-ribosomal P antibody	Number	Percent
Negative	92	92.0
Positive	8	8.0
Total	100	100

Anti-ribosomal P antibody distribution of the studied group and it show that 8(8.0%) had Anti-ribosomal P antibody. Table (7)

Table 8
Distribution of studied sample according to anti-Smith (Sm) antibody

Anti-Smith (Sm) antibody	Number	Percent
Negative	83	83.0
Positive	17	17.0
Total	100	100

Anti-Smith (Sm) antibody distribution of the studied group and it show that 17(17.0%) had anti-Smith (Sm) antibody. Table (8)

Table 9
Distribution of studied sample according to Anti-SSA antibody

Anti-SSA antibody	Number	Percent
Negative	80	80.0
Positive	20	20.0
Total	100	100

Anti-SSA antibody distribution of the studied group and it show that 20(20.0%) had Anti-SSA antibody. Table (9)

Table 10
Distribution of studied sample according to Anti-SSB antibody

Anti-SSB antibody	Number	Percent
Negative	93	93.0
Positive	7	7.0
Total	100	100

Anti-SSB antibody distribution of the studied group and it show that 7(7.0%) had Anti-SSB antibody. Table (10)

Table 11
Distribution of studied sample according to P-ANCA

P-ANCA	Number	Percent
Negative	83	83.0
Positive	17	17.0
Total	100	100

P-ANCA distribution of the studied group and it show that 17(17.0%) had P-ANCA. Table (11)

Table 12
Relation between lupus activity and anti-C1q antibody

	Lupus activity								P value
	No (n=63)		Moderate (n=4)		High (n=23)		Very High (n=10)		
	No.	%	No.	%	No.	%	No.	%	
No	59	93.7	0	0	11	47.8	10	100	<0.001*
Yes	4	6.3	4	100	12	52.2	0	0	

Relation between lupus activity and anti-C1q antibody and it show highly statistically significant differences between lupus activity groups according to anti-C1q antibody. Table (12)

Table 13
Relation between lupus activity and anti-C1q

	Lupus activity				P value
	No (n=63)	Moderate (n=4)	High (n=23)	Very High (n=10)	
Range	7.9 – 10.7	68.9	60.9 – 76.7	65.5	<0.001*
Mean±S.D.	9.29±0.628	68.9	68.97±6.205	65.5	

There was a highly statistically significant difference between lupus activity groups according to anti-C1q with highly increasing in anti-C1q in patients with lupus activity when comparing with patients without lupus activity. Table (13)

Table 14
Relation between Musculoskeletal and anti-C1q

	Musculoskeletal		P value
	No (n=55)	Yes (n=45)	
Range	7.9 – 76.70	9.70 – 65.50	0.067
Mean±S.D.	34.23±30.539	27.10±25.999	

There was no statistically significant difference between musculoskeletal groups according to anti-C1q. Table (14)

Table 15
Relation between Neuropsychiatric lupus and anti-C1q

	Neuropsychiatric lupus		P value
	No (n=55)	Yes (n=45)	
Range	7.9 – 76.70	8.90	<0.001*
Mean±S.D.	39.63±29.628	8.90	

There was a highly statistically significant difference between Neuropsychiatric lupus groups according to anti-C1q with highly decreasing in anti-C1q in patients with Neuropsychiatric lupus when comparing with patients without Neuropsychiatric lupus. Table (15)

Table 16
Relation between Renal and anti-C1q

	Renal		P value
	No (n=55)	Yes (n=45)	
Range	7.9 – 68.90	65.00 – 76.70	<0.001*
Mean±S.D.	21.72±23.442	70.67±5.435	

There was a highly statistically significant difference between Renal groups according to anti-C1q with highly increasing in anti-C1q in patients with Renal when comparing with patients without Renal. Table (16)

Table 17
Relation between Mucocutaneus and anti-C1q

	Mucocutaneus		P value
	No (n=55)	Yes (n=45)	
Range	7.9 – 76.70	65.60 – 76.70	<0.001*
Mean±S.D.	23.85±24.849	71.67±5.037	

There was a highly statistically significant difference between Mucocutaneus groups according to anti-C1q with highly increasing in anti-C1q in patients with Mucocutaneus when comparing with patients without Mucocutaneus. Table (17)

Discussion

Thus, anti-C1q has the potential to accelerate the course of disease (Thanei et al., 2016). One important rationale for the role of C1q and anti-C1q in SLE is based on the so-called “waste disposal” hypothesis. This assumes that SLE is driven by a defective clearance of dying cells that can become antigenic and drive autoimmunity. In fact, C1q has been described to accelerate the clearance of self-antigens generated during apoptosis, and macrophages from C1q-deficient mice and humans show a defective clearance of apoptotic cells in vitro (Taylor et al., 2009). Regarding the demographic data of the studied group, the current study found that age was ranged between 29 – 45 years with mean value 37.50±5.134 years. Male cases were 38(38.0%) while female cases were 62(62.0%).

The current study can be supported by Kianmehr et al., (2020) aimed to compare the diagnostic values of circulating autoantibodies against dsDNA, C1q, C3b, SSA, SSB, and Sm alone or in combination to predict Lupus Nephritis (LN). the study enrolled 40 healthy controls (HCs) and 95 SLE patients with different kidney involvements, including absent (n = 40), inactive (n = 20), and active (n= 35) LN using EIA method. The study showed that the mean ± SD age of the

patients with SLE and HCs was 35.9 ± 11.65 years (range 18 to 71) and 36.2 ± 11.3 years (range 19 to 55), respectively. There were no significant differences in terms of age and gender. The current study showed that disease duration was ranged between 2.8 – 6.8 years with a mean value of 4.40±0.987 years. SLEDAI score was ranged between 0 – 24 with a mean value of 5.62±8.114. The study by Kianmehr et al., (2020) reported that mean disease duration and SLEDAI score for patients with Absent Lupus Nephritis (LN) were 9.8 ± 3.3 years and 6.93 ± 3.3, cases with Inactive LN 8.4 ± 5.3 years and 8.3 ± 3.7, and cases with active LN were 8.1 ± 6.2 years and 19.1 ± 4.1; of note, the disease activity was significantly higher in active LN group as compared to the other groups.

In agreement with our results Soliman et al., (2016) reported that the mean disease duration was 4.2 ± 3 years. For patients with active SLE the mean SLEDAI was 12.56±3.11 and for those with inactive SLE it was 4.01±1.0 with statistically significant difference. Regarding Organ involvement of the studied group, the current study found that in 45(45.0%) the organ involvement was Musculoskeletal, 28(28.0%) the organ involvement was Neuropsychiatric lupus, 19(19.0%) the organ involvement was renal, 16(16.0%) the organ involvement was Mucocutaneus and 8(8.0%) the organ involvement was Hematologic. SLE can affect any organ including the musculoskeletal, skin, hematologic, renal, neuropsychiatric, cardiovascular, and respiratory system (Gergianaki et al., 2018). The following points could be helpful in understanding the disease evolution in real-world setting: First, not all manifestations appear simultaneously and occasionally, a time interval of several months or years may exist between them. In most patients, constitutional (especially fatigue), mucocutaneous and musculoskeletal manifestation represent the earliest complaints (Heinlen et al., 2007). Thus, data from the UK primary care using the Clinical Practice Research Datalink showed that musculoskeletal symptoms were most frequently (58.6%) recorded in the 5 year-period before SLE definitive diagnosis (Nightingale et al., 2017).

Distribution of studied sample according to ACL antibody showed that there were 15(15.0%) had ACL antibody. The study by Chi et al., (2015) reported that in the SLE active group there were 13.7% of patients had ACL antibody and in SLE inactive group, there were 11.4% of patients had ACL antibody. In patients with SLE with renal involvement, there were 11.4% of patients had ACL antibody and in patients with SLE without renal involvement ,there were 13.3% of patients had ACL antibody. Furthermore, Abu-Shakra et al., (1995) enrolled 293 SLE patients and reported that 47% of the patients had an elevated level of anticardiolipin antibodies. In the univariate analysis, elevated anticardiolipin antibody levels were found to correlate with thrombocytopenia ($P = 0.006$), prolonged activated partial thromboplastin time (aPTT) ($P = 0.003$), and positive direct and indirect Coombs' test results ($P < 0.001$). No correlation was identified with any of the clinical features of antiphospholipid syndrome. In the multivariate analysis, anticardiolipin antibodies remained highly associated with thrombocytopenia (odds ratio [OR] 4.05, $P = 0.02$), positive direct Coombs' test (OR 2.31, $P < 0.001$), and prolonged aPTT (OR 1.73, $P = 0.03$). In the multivariate model using venous/arterial thrombosis as the outcome variable, only prolonged aPTT was associated with venous/arterial thrombosis (OR 7.9, $P < 0.001$). None of the laboratory variables were found to correlate with fetal loss.

Regarding the distribution of studied sample according to Anti-C1q antibody and Anti-ds DNA antibody, we found that there were 20(20.0%) had Anti-C1q antibody and 16(16.0%) had Anti-ds DNA antibody. However, Kianmehr et al., (2020) stated that there were (43%) had Anti-C1q antibody and (56%) had Anti-ds DNA antibody in addition to 33% had Anti-C1q + Anti-ds DNA. Furthermore, they reported that more than 75% of SLE patients with severe LN (Class IV) have anti-dsDNA or anti-C1q antibody. The SLEDAI scores were signi¦cantly higher for SLE patients with positive anti-dsDNA (13.5 ± 6.6 vs. 7.7 ± 5.1) and anti-C1q (14.7 ± 6.5 vs. 9.4 ± 5.9) antibodies ($p < 0.001$). Importantly, there was no difference for SLEDAI scores between positive anti-C1q and anti-dsDNA antibodies.

Regarding the distribution of studied sample according to ANA antibody, Anti-ribosomal, anti-Smith (Sm), Anti-SSA antibody, Anti-SSB antibody and P-ANCA, the current study found that there were31(31.0%) had ANA antibody, 8(8.0%) had Anti-ribosomal P antibody, 17(17.0%) had anti-Smith (Sm) antibody, 20(20.0%) had Anti-SSA antibody, 7(7.0%) had Anti-SSB antibody and17(17.0%) had P-ANCA. However, Kianmehr et al., (2020) reported that there were 65% had ANA Positive in SLE absent group, 45% in inactive group and 57 in active group, (28%) had anti-Smith (Sm) antibody, (45%) had Anti-SSA antibody, (21%) had Anti-SSB antibody. While the study by Chi et al., (2015) reported that all cases had ANA antibody, Anti-Smith (Sm) was positive in 23/51 (45.1) in active group vs. 10/44 (22.7) in inactive group. Anti-SSA Ab was positive in 15/51 (29.4) in active group vs. 8/44 (18.2) in inactive group. Anti-SSB Ab was positive in 4/51 (7.8) in active group vs. 4/44 (2.3) in inactive group.

Regarding the distribution of studied sample according to Laboratory investigations. C3 was ranged between 0.45 – 0.99 µg/mL with a mean value of 0.80±0.227 µg/mL. C4 was ranged between 0.11 – 0.19 µg/mL with a mean value of 0.16±0.022 µg/mL. Anti-C1q was ranged between 7.90 – 76.70 AU/mL with a mean value of 31.02±28.668 AU/mL. Ant-dsNDA was ranged between 10.9 – 79.9 IU/mL with a mean value of 36.35±31.907 IU/mL. The study by Kianmehr et al., (2020) reported that the mean hemoglobin in SLE without renal involvement was 12.7 ± 1.3, in inactive LN group was 11.7 ± 2.1 and in active LN group was 10.6 ± 2.8. C3 and C4 in SLE without renal involvement were 125.5 ± 30.1 and 21.6 ± 8.3, in inactive LN group were 120.9 ± 31.1 and 17.4 ± 4.1and in active LN group were 102.9 ± 36 and 16.5 ± 9.5. Serum levels of C3 and C4 were significantly lower in SLE patients with positive anti-C3b and anti-dsDNA antibodies versus the negative ones.

Regarding the relation between lupus activity and anti-C1q antibody the current study found that there were highly statistically significant differences among lupus activity groups according to anti-C1q antibody. The current study also found that there were highly statistically significant differences among lupus activity groups according to anti-C1q with highly increasing in anti-C1q in patients with lupus activity when comparing with patients without lupus activity. In agreement with our results Kianmehr et al., (2020) reported that the frequency and odds ratio of anti-C1q antibody (62.9%, OR= 5.1) was significantly higher in the active LN group compared with both inactive and absent LN groups. Moreover,

the levels of anti-C1q antibodies positively correlated with disease activity in patients with SLE.
In addition, Chi et al., (2015) reported that Anti-C1q antibodies were strongly associated with disease activity and LN in SLE patients. Furthermore, Bock et al., (2015) reported that Anti-C1q antibodies were found to strongly correlate with parameters of SLE disease activity. Similarly, Shang et al., (2021) enrolled 114 SLE patients, and found that Anti-C1q antibody was significantly higher in SLE than other autoimmune disease patients ($p < 001$), active LN than non-renal SLE patients ($p < .05$), and higher in SLE patients with moderate and severe disease activity than mild disease activity ($p < .01$). Serum level of Anti-C1q antibody was correlated with SLE disease activity index (SLEDAI) ($p < .05$). Anti-C1q antibodies were strongly associated with lupus disease activity in SLE patients, suggesting that it may be a reliable, sensitive and non-invasive serological marker for identification of SLE patients with active SLE disease. Further studies with larger sample size are needed to assess the risk factors of this disease and to find compare the sensitivity of this biomarker with other biomarkers.

Conclusion

Anti-C1q antibodies were strongly associated with lupus disease activity in SLE patients, suggesting that it may be a reliable, sensitive and non-invasive serological marker for identification of SLE patients with active SLE disease.

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