Serum complements and immunoglobulin profiles in systemic lupus erythematosus patients: An observational study at a teaching hospital

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ABSTRACT

Context: Serum complement proteins and autoantibodies play an important role in the pathogenesis and diagnosis of systemic lupus erythematosus (SLE). Abnormalities in various immunoglobulin levels are described in patients of SLE. **Aims:** To study the spectrum of clinical manifestations and measure the serum levels of complement C3, complement C4, autoantibodies and immunoglobulin G (IgG) in patients of SLE and compare with healthy controls. **Settings and Design:** The present study is a prospective hospital-based observational study conducted between May 2014 and December 2018. **Statistical Analysis Used:** Unpaired t-test was used to compare the mean values between the SLE patients and healthy controls. **Material and Methods:** A total of 100 cases of SLE and 100 healthy controls were included in the study. The clinical data were retrieved. Serum antinuclear antibody, anti-ds DNA antibody, and anti-Smith antibody levels, and complements C3, C4 and IgG were measured. **Results:** Arthritis (89%) and anaemia (65%) were two common clinical presentations. The low complement C3 levels and C4 were detected in 64 and 62% of the SLE patients. Serum IgG was increased in 41% of the patients. A reduced level of IgG was detected in 6% of the patients. **Conclusion:** Primary care physicians should be aware of the clinical and serological manifestations of SLE as early detection will reduce end-organ damage. Autoantibody testing and complement testing should be done in all suspected cases. This study showed a significantly reduced C3 and C4 and elevated IgG in many cases of SLE as compared to control. Hypogammaglobulinemia was also present in a minority of the cases.

Keywords: Complement C3, complement C4, immunoglobulin, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic disease associated with the formation of autoantibodies and activation of the complement system which leads to tissue damage.[1] In India, there is a paucity of rheumatologists, while the disease burden is gradually increasing. The primary care physician should be aware of the essential serological tests like antinuclear antibody (ANA) for diagnostic purposes and complements for disease activity. Only the diagnosed patients might then be referred to tertiary care centres for treatment. The consumption of complement leads to low serum levels of C4 and C3 in SLE patients. Due to the clinical relevance of complement levels in SLE, the new classification criteria developed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) includes low plasma complement (C3, C4, CH50) as one

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of the diagnostic criteria.[2] Hypergammaglobulinemia and hypogammaglobulinemia both were described in the SLE patients.[3,4] B-cell targeted therapy with rituximab is indicated in SLE with refractory disease. A few studies advocate the measurement of serum immunoglobulin levels to detect hypogammaglobulinemia before starting B-cell targeted therapy like rituximab, as it further induces hypogammaglobulinemia.[5] The aim of our study is to measure the serum levels of complement C3, complement C4, IgG and autoantibodies like ANA, anti-double-stranded DNA antibody (anti-dsDNA) and anti-Smith (Sm) antibody in patients of SLE and healthy controls.

Materials and Methods

The present study is a hospital-based prospective observational study conducted between May 2014 and December 2018. A total of 100 patients of SLE and 100 healthy age and sex-matched controls were included in the study. The patients who visited the rheumatology OPD units of the Department of Medicine were evaluated for SLE. In all the cases, clinical details and blood samples were taken after obtaining consent from the patients. The study was conducted after obtaining ethical approval from the Institute Ethics Committee (letter no 2014-15/EC/1193). Inclusion criteria: All patients diagnosed as SLE by the revised 1997 American College of Rheumatology (ACR) criteria were included in the study. Exclusion criteria: The patients taking immunosuppressive drugs were excluded from the study. Sample collection: Four millilitres of blood was taken in a plain vial for immunoglobulin, complement, ANA, anti-dsDNA antibody and anti-Sm antibody estimation. The serum sample was stored at −70°C.

Estimation of ANA and anti-dsDNA

Semiquantitative estimation of the serum level of antinuclear antibodies was done by an indirect non-competitive enzyme immunoassay ANA Kit of Euro Diagnostica, Sweden. The quantitative estimation of anti-dsDNA antibodies was done by an indirect non-competitive enzyme immunoassay dsDNA Kit of Euro Diagnostica, Sweden.

Complement and immunoglobulin estimation

Immage 800 protein chemistry analyser of Beckman Coulter, USA, was used for the estimation of complement and IgG by the nephelometry method. C3 and C4 estimation were done by Complement C3 and C4 Kits of Beckman Coulter. The reference range of C3 is 80–160 mg/dL and C4 is 10–40 mg/dL in our laboratory. The IgG estimation was done by Human Immunoglobulin IgG Kits of Beckman Coulter by the nephelometry method. The reference value of IgG is 600–1600 mg/dL in our laboratory. The detection of IgG autoantibodies against the Sm antigens was done by D-tek BlueDriverDot ANA8 IgG Immunodot kit (D-tek, Mons, Belgium). The test is based on the principle of enzyme immunoassay.

Statistical analysis

All statistical analyses were performed using SPSS version 20. Unpaired t-test was performed to find the statistical significance between the mean and standard deviation of immunoglobulin, complement of patients and healthy controls. The Chi-square test was used to find out the significance between the categorical data of two groups. A *P* value of less than 0.05 (*P* < 0.05) was considered statistically significant.

Results

A majority of our patients were females (*n*: 82, 82%) in our study with the female: male ratio of 4.6:1. In the control group, 64 were females and 36 were males. The age-wise distribution of patients and controls is shown in Table 1. The highest number of SLE cases (37.0%) was seen in the age group of 21–30 years. The mean age of the SLE patients was 31.67 ± 10.09 years with the age range from 6 to 65 years. The frequency of various clinical features in the SLE patients is listed in Table 2. Arthritis was the most common clinical presentation (89%) of SLE in our study. Renal involvement was seen in 42% of the cases. Abnormalities in the haematological parameters were seen in 67 (67%) cases. Anaemia was present in 65 (65%) patients, followed by lymphopenia in 25 cases. Leucopenia was noted in 10 cases and thrombocytopenia in 8 cases. Haemolytic anaemia was seen in only two cases. The occurrence of ANA, anti-ds DNA antibody and anti-Sm antibody in patients and controls is shown in Table 3. In our study, 96% of the cases were positive for ANA, 32% of the cases were positive for anti-dsDNA and anti-Sm Ab was detected in only 33% of the cases. The rise of ANA, anti-dsDNA and anti-Sm antibody in SLE was statistically significant as compared to control. In healthy controls, ANA was detected in six cases while anti-dsDNA or anti-Sm Ab was not detected.

The serum levels of C3 and C4 in the SLE patients and controls are shown in Table 4. Sixty-four (64%) patients had reduced C3 levels and 36 (36%) patients had values within the normal range. The comparison between the mean values showed that the SLE patients had significantly reduced serum C3 levels as compared to controls (*P*-value < 0.001). The reduced value of C4 levels was detected in 62 (62.0%) SLE patients. The C4 levels were within the normal range in 38 (38.0%) cases and none of the patients had elevated C4 values. The mean value of C4 was significantly

Table 1: Age-wise distribution of SLE patients and control

Age groups of patients (years)	SLE (*n*=100)		Control (*n*=100)	
	No	**%**	**No**	**%**
<20	14	14.0	14	14.0
21-30	37	37.0	63	63.0
31-40	32	32.0	18	18.0
41-50	14	14.0	5	5.0
>50	3	3.0	0	0.0
Mean±SD	31.67±10.09		25.95±9.17	

Table 2: Frequency of various clinical manifestations in SLE

Symptoms	SLE (*n*=100) *n* (%)
Malar rash	41 (41%)
Discoid rash	19 (19%)
Photosensitivity	55 (55%)
Oral ulcer	41 (41%)
Arthritis	89 (89%)
Pleuritis	21 (21%)
Pericarditis	2 (2%)
Nephritis	42 (42%)
Neuropsychiatric	15 (15%)
Haematological abnormalities	67 (67%)
Fever	54 (54%)
Alopecia	61 (61%)

Table 3: Antinuclear antibody (ANA), anti-dsDNA antibody and anti-Sm antibody positivity in SLE patients and controls

Groups	No (%)		
	ANA	Anti-dsDNA	Anti-Sm
A. Control (100)	6 (6.0)	0 (0.0)	0 (0.0)
B. SLE (100)	96 (96.0)	32 (32.0)	33 (33.0)
A vs. B			
χ^2	162.065	38.095	39.521
P	<0.0001*	<0.0001*	<0.0001*

*Statistically significant (P<0.05)

Table 4: Serum complements C3 and C4 levels in SLE patients and controls

Study group (no. of cases)	Serum C3 value (mg/mL)			Mean±SD	A vs. B	
	<80	80-160	>160		*t*	*P*
A. SLE (100)						
n	64	36	0	90.62±41.44	6.072	<0.0001*
%	64.0	36.0	0.0			
B. Control (100)						
n	02	89	09	127.51±44.42		
%	02.0	89.0	9.0			

Study group (no. of cases)	Serum C4 value (mg/mL)			Mean±SD	A vs. B	
	<10	10-40	>40		*t*	*P*
A. SLE (100)						
n	62	38	0	16.39±11.84	3.449	0.0007*
%	62.0	38.0	0.0			
B. Control (100)						
n	08	88	04	21.49±8.86		
%	08.0	88.0	4.0			

*Statistically significant (P<0.05)

reduced in SLE (*P*-value 0.001) as compared to controls. The correlation between serum C3 and C4 levels with the gender of the patients is shown in Table 5. There was no significant difference in the mean serum C3 and C4 in the female and male patients of SLE, although more percentage of female patients had reduced C3 levels (65.9%) as compared to males (55.6%).

The serum levels of IgG are shown in Table 6. Eight (8%) patients of SLE had IgG levels below 600 mg/dL and 41 (41%) patients had elevated serum IgG. The elevation in serum IgG in the SLE patients (*P*-value < 0.001) was statistically significant as compared to controls. All the controls had normal levels of serum IgG. There was no significant difference in the mean value of the serum levels of IgG in the female and male patients of SLE. The correlation between gender and serum IgG levels is shown in Table 7.

Discussion

SLE is a systemic disease which is seen in all age groups but is more common in young adults. In our study, a majority of SLE patients (69%) are between 21 and 40 years of age. The mean age of presentation is 31.67 years. The mean age of SLE patients in different studies varied from 21.6 to 31 years. Malaviya *et al.*[6] and Saigal *et al.*[7] from India reported a lower mean age of presentation: 24 and 27.9 years, respectively. Paul *et al.*[8] from India reported the lowest mean age of 21.6 years. Masi *et al.*[9] from the United States reported a mean age of 31 years which is very much close to our study. It has long been observed that SLE mostly affects females. In our study, the female to male ratio was 4.6:1. Masi *et al.*[9] reported a female to male ratio of 5.5:1, which is close to our study findings. In contrast to our study, other workers from India reported a much higher prevalence of SLE in females. Malaviya *et al.*[6] from New Delhi reported a female to male ratio of 8:1, while in the study of Saigal *et al.*[7] from Rajasthan, it was 11:1. Paul *et al.*[8] from Kerala reported a high female to male ratio of 19:1. One study from northeast India reported a very high female to male ratio of 28:1.[10] A recent Indian study in a large cohort of adult SLE patients reported the female to male ratio of 13:1.[11]

In the present study, arthritis was the most common (89%) clinical manifestation of SLE. One previous study by Paul *et al.*[8] found it in 89.3% of the cases. Fever was present in 54% of the cases of SLE in the present study. Similar results were seen in a study done by Madhavan *et al.*[12] Pattanaik *et al.*[11] reported a very high incidence of fever in 75.3% of adult SLE patients. Paul *et al.*[8] noted fever in only 4% of the patients and Saigal *et al.*[7] found it in 6.7% of the cases. Malar rashes were found in 41% of the cases, which was more or less similar to the findings of the previous studies.[6,8,12] Photosensitivity was found in 55% of the cases of SLE in the present study. Madhavan *et al.*[12] 1988, reported it in 52% of the cases. The oral ulcer was also a very common manifestation in SLE. In the present study, it was found in 41% of the cases but Saigal *et al.*[7] and Paul *et al.*[8] found it in 64 and 61% of the cases, respectively. Malaviya *et al.*[6] and Madhavan *et al.*[12] found it in low frequency. Pleuritis was noted in 21% of the SLE cases in the present study, while the other studies reported it in a low frequency varying from 8 to 17%.[6-8,10,12] Alopecia was observed in 62% of the SLE cases, which was more or less similar to the findings of other studies.[7,8] Malaviya *et al.*[6] reported alopecia in a very high frequency (82%) in the SLE patients. Nephritis was observed in 42% of the cases in our study but Malaviya *et al.*[6]

Table 5: Correlation of serum complements C3 and C4 levels with gender in SLE patients

Gender of SLE patients	Serum C3 value (mg/mL)			Mean±SD	A vs. B	
	<80	80-160	>160		t	P
A. Female (82)						
No	54	28	0	88.46±41.63	1.115	0.268
%	65.9	34.1	0.0			
B. M ale (18)						
No	10	8	0	100.47±40.27		
%	55.6	44.4	0.0			

Gender of SLE patients	Serum C4 value (mg/mL)			Mean±SD	A vs. B	
	<10	10-40	>40		t	P
A. Female (82)						
No	51	31	0	16.16±11.81	0.427	0.670
%	62.2	37.8	0.0			
B. Male (18)						
No	11	7	0	17.48±12.23		
%	61.1	38.9	0.0			

Table 6: Serum IgG levels in SLE patients and controls

Study group (no. of cases)	Serum IgG levels (mg/dL)			Mean±SD	A vs. B	
	<600	600-1600	>1600		t	P
A. SLE (100)						
n	08	51	41	1811.27±1401.38	4.117	<0.0001*
%	8.0	51.0	41.0			
B. Control (100)						
n	00	100	00	1230.94±151.63		
%	0.0	100.0	0.0			

*Statistically significant ($P<0.05$)

Table 7: Correlation of IgG levels with gender in SLE patients

Gender of SLE patients	Serum IgG value (mg/dL)			Mean±SD	A vs. B	
	<600	600-1600	>1600		t	P
A. Female (82)						
n	5	46	31	1784.71±1449.97	0.403	0.688
%	6.1	56.1	37.8			
B. M ale (18)						
n	3	5	10	1932.27±1183.32		
%	16.7	27.8	55.6			

found it in 73.1% of the cases, which was higher than the present study. Madhavan *et al*.[12] found it in 38.8% of the cases and Paul *et al*.[8] reported it in 33.3% of the cases. Joo *et al*.[13] reported renal involvement in 42% of the patients in a study of a large Asian cohort. Pattanaik *et al*.[11] reported nephritis in 48.6% of the adult SLE patients. The neuropsychiatric manifestation was noted in 15% of the cases. Findings similar to our study were seen in one previous study.[6] The haematological abnormalities were detected in 67% of the cases. Anaemia was the most frequent haematological abnormality (65%). A similar proportion of

haematological abnormalities was seen in a study by Talukdar *et al*.[10] In the present study, anaemia is the second most common clinical presentation of SLE. Anaemia due to iron deficiency is also quite prevalent in the young Indian female population. So the primary care provider should be alert, otherwise, the diagnosis of SLE can be missed.

The incidence of ANA in the general healthy population varies from 5.92% in the Chinese population to 30.8% in the Afro-American population.[14,15] Our study results (6%) are close to a study done in the Chinese population. This 6% of healthy controls, which were positive for ANA had no clinical symptoms. It is important for the primary care physician to be aware of the fact that antinuclear antibodies can be seen in normal healthy individuals as found in the present study. The diagnosis of SLE should not be suspected only on the basis of a positive ANA test, in the absence of clinical symptoms. Similarly, ANA can be negative in the case of lupus due to multiple reasons like technical limitations, immune-complex-bound ANA or prozone effect. So, if the clinical features of SLE are present with negative ANA, the primary care physician can still suspect SLE, and they can later repeat the antibody tests in follow up. The presence of ANA is the immunological hallmark of SLE. In clinical practice, ANA testing is often used as a part of primary investigation. ANA positivity in an SLE patient varies from 93.3 to 100%.[6-8,10,16] In our study, we also found 96% anti-ANA positivity in SLE patients. Two recent studies, one from Greece and the other from Korea reported 93.7 and 97.8% ANA positivity in the SLE patients.[17,18] Anti-dsDNA antibodies were detected in 32% of the cases in our study. In different studies, the frequency of anti-dsDNA varied from 43 to 92%, with the specificity varying from 89 to 99%.[12,19-23] These authors also found that anti-dsDNA correlates with disease activity. In contrast to these studies, we found a very low frequency (32%) of anti-dsDNA positivity. Similar to our findings, Faria *et al*.[24] from Brazil reported the frequency of anti-dsDNA in 32% and Nikolopoulos *et al*.[17] reported it in 36.6% of the patients. Anti-Sm antibodies are present in 15–55.5% of the cases of SLE patients.[19,20,25,26] The frequency of anti-Sm Ab varies from 21 to 35% in different Indian studies.[6,10,12] In the present study, we found positivity in 33% of the cases. A wide variation in the presence of anti-dsDNA and anti-Sm antibodies is due to the different techniques used for the detection of these antibodies. The main utility of the anti-Sm antibody is in the diagnosis of SLE when the anti-dsDNA antibody is absent. It has been observed that in around 14.8% of the SLE cases, where anti-dsDNA antibody was absent but anti-Sm antibody was present, thus, confirming SLE.[27] Similarly, in our study, 15% of the SLE patients had anti-Sm antibody but anti-ds DNA antibody was absent. The above findings of our study suggest that when a primary care physician has a strong clinical suspicion of SLE but the ANA is negative, in those cases, the anti-dsDNA and anti-Sm antibodies may help in the diagnosis. The primary care physician may keep these suspected SLE patients with negative ANA in the follow-up and the ANA can be repeated later with different kits and techniques.

In the present study, reduced levels of C3 were detected in 64.0% of the cases and C4 was reduced in 62.0% of the cases of SLE. Jallouli *et al.*[22] also found C3 deficiency in 63.5% and C4 in 73.4% of the patients of SLE. Elwy *et al.*[28] and Li *et al.*[29] also reported the mean levels of C3 and C4 significantly reduced in SLE as compared to healthy controls. The present study findings further confirm that a simple serological test like the measurement of serum complements helps in the diagnosis of SLE by the primary care physician.

In our study, 41 (41%) patients had IgG levels above 1600 mg/dL. The mean level of IgG was significantly elevated in SLE patients compared to healthy controls. Many previous studies have also reported an increased level of IgG in SLE patients.[3,30,31] In our study, we also found eight (8%) patients with hypogammaglobulinemia (IgG <600 mg/dL). A study by Cuadrado *et al.*[3] also observed reduced IgG level in 8.4% of the SLE patients. B-cell targeted therapy with rituximab can itself cause hypogammaglobulinemia in SLE patients with normal pretreatment immunoglobulin levels and increase the risk of infection. In SLE patients with reduced levels of immunoglobulins before treatment, rituximab can further reduce the immunoglobulins and potentially increase the risk of infection. Therefore, it is important to estimate the serum IgG levels in the SLE patient before starting the therapy with rituximab.

Limitations: The demographic data of the study cannot be generalised, since it is a single-centre study with a limited sample size.

Conclusion

Our study reveals that arthritis and anaemia are the two most common clinical manifestations of SLE. Antinuclear antibodies can be seen in normal healthy individuals. Hence, the diagnosis of SLE should not be suspected only on the basis of a positive ANA test in the absence of clinical symptoms. Anti-smith antibody is diagnostically helpful in SLE, especially in those cases which are negative for anti-dsDNA antibodies. In our study, serum complement C3 and complement C4 levels were significantly reduced in the SLE patients. This further establishes the role of complements in the pathogenesis of SLE and tissue injury. The complements are not only useful in the diagnosis of SLE, but they can also alert the physician towards disease progression. None of the patients included in the study had received immunosuppressive treatment, and serum immunoglobulin IgG was elevated in many of them. It suggests that SLE is associated with the activation of B-lymphocytes, which leads to increased production of serum IgG. Around 8% of the patients in our study had low serum IgG levels, so we suggest measuring pretreatment immunoglobulin levels to rule out hypogammaglobulinemia in the patients of SLE before starting B-cell targeted therapy.

Key messages

Apart from nephritis and arthritis, anaemia is also a very common presentation of SLE.

ANA positivity can be seen in some healthy individuals so indiscriminate ANA testing should be avoided.

In patients with clinical suspicion of SLE and negative ANA, the physician should repeat antibody tests on follow-up as not all features of SLE will appear simultaneously.

Reduction of serum complements C3 and C4 is seen in many patients of SLE. Routine measurement of serum complements helps in diagnosis and predicting flare-ups of SLE.

Both elevated and reduced levels of serum IgG were detected in SLE. The measurement of serum IgG should be done before starting B-cell targeted therapy to rule out hypogammaglobulinemia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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