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Complement levels and risk of organ involvement in patients with systemic lupus erythematosus

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To cite: Gandino IJ, Scolnik M, Bertiller E, *et al*. Complement levels and risk of organ involvement in patients with systemic lupus erythematosus. *Lupus Science & Medicine* 2017;**4**. doi:10.1136/lupus-2017-000209

Received 19 January 2017
Revised 3 May 2017
Accepted 7 May 2017

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ABSTRACT

Objective Complement plays a major role in SLE. Complement participation has been linked to disease activity and damage. Our objective was to estimate the association of complement behaviour with clinical manifestations, visceral injury and mortality in patients with SLE.

Methods Complement determinations (C3 and C4 levels) were analysed in patients with SLE (fulfilling American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC)criteria) seen at a university hospital between 2000 and 2013. Patients were grouped in those with permanent C3 and/or C4 low values (low complement group), those with C3 and C4 constant normal values (normal complement group) and those with fluctuant values (periods of normal and periods of low values: fluctuant group). Clinical characteristics and mortality were analysed and compared between groups.

Results 270 patients with SLE were included (242 females, 89.6%), mean age at diagnosis was 34.2 years (SD 15.8). 75 patients had fluctuant levels of complement, 79 patients had persistent low complement levels and 116 had normal complement levels. Lupus glomerulonephritis was more frequent in patients with fluctuant levels (75%, 56% and 49%, respectively, p=0002). The normal complement group had less frequency of haematological involvement and anti-double stranded DNA (dsDNA) antibodies. At the end of the follow-up, 53% of the patients had damage (SLICC/ACR ≥1). In a Cox proportional hazard model age at diagnosis, neurological impairment, thrombocytopaenia and corticosteroids were associated with more damage, while hydroxychloroquine was a protective factor. There were no differences between complements groups on accumulated damage. Ten-year survival rate was 93%, 93.5% and 92% for the normal complement group, the persistently low group and the fluctuant group, respectively.

Conclusions Patients with constant normal complement had lower prevalence of haematological involvement and anti-dsDNA, while patients with fluctuant complement had higher renal impairment. Neither the persistent low complement nor the fluctuant complement groups had increased mortality and/or visceral damage.

INTRODUCTION

SLE is a chronic autoimmune disease characterised by a large number of autoantibodies and fluctuating disease activity that results in tissue damage and potentially life-threatening multiorgan failure.[1] The incidence of SLE is variable but generally estimated to be about 1–10 per 100 000 person-years with a prevalence of 20–70 per 100 000 according to the different parts of the world. It is about 10 times more frequent in women.[2–4]

The complement system is an important effector pathway of innate immunity and plays a major role in SLE.[5] Complement participation may occur in at least two ways. First, deficit of some components has been implicated as a risk factor for disease development.[5 6] In particular, complete deficiency of classical pathway complement component C1 has been associated with an elevated risk of SLE in up to 90% of individuals with this condition.[7 8] Other complement components such as C2 and C4 have also been associated.[8] Second, the intense activation of complement has been linked to disease activity and damage to certain organs.[5 6] Many complement products have been assigned different degrees of clinical value in assessing disease activity, such as serum CH50, levels of C3, C4, C3d, C4d, C3a, C4a, C5b–9, Ba, Bb and urine C3d.[6 9 10]

Our objective was to estimate the impact of complement level changes on clinical manifestations, visceral injury and mortality in our patients with SLE, with special interest in patients with continuous low complement levels compared with patients with fluctuating and/or continuous normal levels.

METHODS

We retrospectively included all patients with lupus who were seen at the Hospital Italiano de Buenos Aires from year 2000 to 2013. The inclusion criteria were fulfilment of American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria, 18 years of age or older and at least two C3 and C4 determinations, measured by nephelometry, during

follow-up. Low C3 was defined when serum levels were lower than 83 mg/dL and low C4 when serum levels were lower than 10 mg/dL.

Patients were divided in three groups: those with persistent normal complement levels (all measurements above normal levels), those with persistent low complement levels (all measurements below normal levels) and finally those with fluctuant complement levels (at least one normal measurement and at least one low measurement).

The following outcomes were compared between the three groups: clinical features, damage at the end of follow-up (measured by SLICC/ACR damage index) and mortality.

Renal involvement was defined as renal failure and/or microhematuria and/or proteinuria (>500 mg/24 h) plus biopsy that shows lupus patterns. Neurological involvement was defined as the presence of psychosis, seizures, myelitis, multiple mononeuritis, acute confusional syndrome and peripheral or cranial neuropathy that could not be explained by other reason. Leucopaenia, lymphopaenia and thrombocytopaenia were defined as cell counts <4000 cell/mm^3<1000 cell/mm^3 and <100000 cell/mm^3, respectively, that could not be explained by other means. Haemolytic anaemia was defined as anaemia with haemolytic parameters (rise of indirect bilirubin and lactate dehydrogenase, and/or haptoglobulin declines) plus positive Coombs test. Drugs (hydroxychloroquine, corticosteroid pulse, corticosteroid, immunosuppressive therapy (cyclophosphamide, mycophenolate, azathioprine) and biological therapy (rituximab and belimumab)) were defined as dichotomy variable (received/nor received) at any time during follow-up.

Statistical analysis was performed with the STATA program V.14.1. Continuous variables were computed as mean and SD or median with IQR, depending on the distribution of the variable. Categorical variables were presented as number and percentage. Analysis of variance test was used to compare continuous variables. χ^2 and Fisher tests were used to compare categorical variables. A Cox proportional hazard model was used to estimate the association between complement level group and mortality or organ damage, adjusting by age, sex, disease duration, organs involvement, haematological involvement, drugs used and anti-dsDNA. A p value of <0.05 was considered significant.

RESULTS

We included 270 patients, 242 (89.6%) females with a mean age at diagnosis of 34.2 years (SD 15.8) (table 1). One hundred and sixteen patients (43%) had persistently normal complement, 79 patients (29%) had persistently low complement levels and 75 patients (28%) had fluctuant levels. The median of complement determinations throughout the follow-up period was 7 (range:2–23) without differences among complement groups. Only 43 (16%) patients were classified based on only two samples.

Table 1 shows cumulative clinical manifestations in the three groups. The only significant difference were

Table 1 Patients demographic, cumulative clinical data and autoantibodies profile by complement group

	Normal complement (n=116)	Persistent low complement (n=79)	Fluctuant complement (n=75)	p Value
Females, n (%)	107 (92.2)	70 (88.6)	65 (86.7)	0.439
Age at diagnosis, mean, years (SD)	36.4 (16.5)	32.4 (14.7)	32.7 (15.8)	0.1397
Follow-up, median, years (IQR)	6.4 (8.2)	6.1 (7.6)	9.2 (5.6)	0.345
Mean age at end follow-up (SD)	43.5 (17.3)	38.5 (15.3)	41.9 (15.4)	0.394
Cutaneous lupus, n (%)	76 (65.5)	50 (63.3)	44 (58.7)	0.773
Oral ulcers, n (%)	24 (20.7)	19 (24.1)	20 (26.7)	0.624
Serositis, n (%)	37 (31.9)	15 (18.9)	17 (22.7)	0.102
Arthritis, n (%)	59 (50.9)	47 (59.5)	35 (46.7)	0.261
Neurological involvement, n (%)	15 (12.9)	7 (8.9)	7 (9.3)	0.598
Renal involvement, n (%)	57 (49)	44 (56)	56 (75)	0.002
Leucopaenia and/or lymphopaenia, n (%)	35 (30.2)	39 (49.4)	34 (45.3)	0.007
Thrombocytopaenia n (%)	20 (17.2)	28 (35.4)	25 (33.3)	0.026
Haemolytic anaemia n (%)	2 (1.7)	7 (8.9)	6 (8)	0.057
ANA positive, n (%)	109 (94)	77 (97.5)	68 (90.7)	0.202
Anti-dsDNA positive, n (%)	52 (44.8)	54 (68.3)	57 (76)	<0.001
Anti-Sm positive, n (%)	12 (10.3)	10 (12.7)	8 (10.7)	0.882
Lupus anticoagulant positive, n (%)	14 (12.1)	16 (20.2)	11 (14.7)	0.254
Anticardiolipins positive, n (%)	17 (14.7)	20 (25.3)	13 (17.3)	0.405

Table 2 Univariate and multiple Cox regression analysis with damage (SLICC/ACR ≥1) as dependent variable, adjusting by patients' characteristics and treatment.

	Univariate Cox regression			Multiple Cox regression		
	HR	95% CI	p Value	HR	95% CI	p Value
Age at diagnosis	1.01	0.99 to 1.02	0.052	1.01	1.006 to 1.03	0.002
Sex	1.45	0.89 to 2.35	0.131	1.3	0.76 to 2.21	0.325
Renal impairment	1.06	0.76 to 1.49	0.695	1.08	0.73 to 1.59	0.685
Neurological impairment	1.57	1.005 to 2.46	0.047	1.78	1.05 to 3.02	0.03
Leucopaenia or lymphopaenia	1.003	0.72 to 1.39	0.983	0.92	0.65 to 1.31	0.651
Thrombocytopaenia	1.46	1.03 to 2.07	0.031	1.79	1.21 to 2.63	0.003
Haemolytic anaemia	1.09	0.55 to 2.15	0.794	0.97	0.47 to 2.02	0.954
Persistent low complement	1.29	0.86 to 1.92	0.204	1.29	0.83 to 2.01	0.257
Fluctuant complement	0.83	0.56 to 1.24	0.384	0.67	0.42 to 1.05	0.081
Hydroxychloroquine	0.67	0.41 to 1.109	0.121	0.37	0.21 to 0.66	0.001
Corticosteroid pulse	1.17	0.83 to 1.66	0.358	1.05	0.64 to 1.70	0.843
Corticosteroid	1.6	0.78 to 3.28	0.193	2.34	1.01 to 5.42	0.046
Immunosuppressive drugs (cyclophosphamide, mycophenolate and azathioprine)	1.5	1.07 to 2.105	0.018	1.57	0.99 to 2.48	0.052
Biological therapy (rituximab and belimumab)	1.38	0.74 to 2.57	0.301	1.14	0.59 to 2.18	0.693
Anti-dsDNA	1.12	0.8 to 1.57	0.5	1.05	0.74 to 1.50	0.758

SLICC/ACR, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus.

renal impairment, more frequent in the fluctuant group, leucopaenia, lymphopaenia and thrombocytopaenia and anti-double stranded DNA antibodies (dsDNA), more frequent in the fluctuant and persistently low complement groups.

Regarding damage at the end of the follow-up, 53% of the patients had SLICC/ACR equal to or greater than one. When Cox proportional hazard models were used (table 2) age at diagnosis, neurological impairment, thrombocytopaenia and corticosteroids were associated with more damage (HR 1.01; 1.78; 1.79; 2.34, respectively). Hydroxychloroquine (HCQ) behaved as a protective variable (HR 0.37; IC 95% 0.21–0.66; p< 0.001). None of the complement groups were associated with accumulated damage.

Fourteen (6%) patients died. There were no significant differences on survival between the three complement groups. At 10 years survival was 93%, 93.5% and 92% for the normal complement group, the persistently low group and the fluctuant group, respectively. Six patients died because of infections, three died because of lupus activity and five died from other causes (cancer, unknown). In the fluctuant group almost all causes of mortality were infections, whereas in the persistently low group, they were equally divided between infections and activity and in the normal group, mortality was associated with other causes. There were significant differences in mortality causes between the fluctuant and the normal groups (p=0.008).

We analysed the different variables and their influence on mortality. We found that HCQ was a protective variable (HR 0.18; 95% CI 0.039 to 0.92; p=0.040), while thrombocytopaenia (HR 3.2; 95% CI 1.005 to 10.3; p=0.049) and age at diagnosis (HR 1.07; 95% CI 1.03 to 1.1; p<0.001) were associated with increased mortality risk. The presence of anti-dsDNA was not associated with increased mortality (HR: 0.34; 95% 0.09 to 1.23; p=0.100). The different complement groups were not associated with mortality.

DISCUSSION

This paper compares the characteristics of lupus patients according to serum complement levels, to ascertain whether differences in these levels may explain different course or clinical characteristics. This approach may be unique in that we divided groups according to normal complement levels, persistently low complement levels and fluctuant complement levels.

There is recognition that complement levels and SLE are intimately associated, but there still is controversy regarding the value of serum C3 and serum C4 as biomarkers of lupus disease activity.[9–19] Although we found, as in other reports, that decreased levels of serum C3 and C4 were observed in patients with renal and haematological disease,[20] our work revealed that behaviour of complement levels is heterogeneous in SLE.

Damage at the end of follow-up occurred in 53% of the patients, and we did not find differences between complements groups. This is similar with the findings of Petri *et al*,[21] who did not find an association between complement consumption and damage. The strongest predictors of damage in their study appeared to be age and current corticosteroid dose.

Like in other series, the 10-year survival rate was nearly 90%,[22] and according to our results, complement behaviour did not seem to influence survival. It was interesting, however, to note that in the fluctuant complement group almost all deaths were due to infections, in the persistently low group they were equally distributed between infections and disease activity and in the normal group they were all from other causes neither related to infections nor to lupus activity. These findings may suggest that patients with fluctuant and persistently low level complement had more active disease and might have received more immunosuppressive therapy.

We found that HCQ was a protective factor both for mortality and damage, similar to other series.[23–26] However, thrombocytopaenia was a mortality risk factor, in agreement with two large and long-term studies.[27 28] Other studies, however, have shown no influence of thrombocytopaenia on survival.[29 30] Thrombocytopaenia may therefore be debatably regarded as a prognostic indicator of reduced survival.[31] As in other studies older age at diagnosis was a death risk factor.[32 33]

A limitation of this study is that we did not correlate disease activity with complement levels. Another limitation is that in the persistently low complement group, we did not divide the patients into those who only had low C3 or low C4, so low levels could have been due to congenital complement deficit. However, the proportion of patients with low complement values due to deficit and not to disease activity is low in the literature.[8] Related to drugs use, we did not determinate doses and periods of times because records were incomplete for these data.

In summary, our data suggest that patients with persistently normal levels of complement have lower prevalence of leucopaenia, lymphopaenia, thrombocytopaenia and antibodies to dsDNA. However, patients with fluctuant complement levels have higher renal impairment. Persistently low complement or fluctuant complement level did not increase visceral damage and/or mortality in these patients.

Contributors All authors contributed to the conception and design of the study, acquisition and/or interpretation of data, drafting the article or revising it critically for important intellectual content and approved the final version of the manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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