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Association of damage with autoantibody profile, age, race, sex and disease duration in systemic lupus erythematosus

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Objective. **To determine if there is any association between autoantibody profile and damage in a cohort of patients with systemic lupus erythematosus (SLE).**
Methods. **A prospective cohort of SLE patients attending two SLE clinics in Birmingham was analysed. All patients fulfilled ARA criteria for SLE. Detailed clinical and serological information was recorded at each visit. Damage according to the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) was recorded 6-monthly and the last score in the year 2000 or prior to death was used in the analysis. Univariate analysis was performed with the χ^2 test, Fisher's exact test or univariate analysis of variance. Multivariate analysis was done with binary logistic regression.**
Results. **A total of 348 patients (326 females) were studied, comprising 208 Caucasians, 65 Afro-Caribbeans, 59 Asians, four Orientals and 12 others. There were 32 (9.2%) deaths and 156 (44.8%) patients had damage recorded during follow-up. The presence of damage showed no significant association with race, sex or anti-cardiolipin, anti-Ro, anti-La, anti-Sm, anti-RNP and anti-dsDNA antibodies. Only age, disease duration and other antibodies to extractable nuclear antigens (ENA) were found to be associated with the presence of damage. When individual organ damage was analysed, the only significant associations were of anti-Ro with ocular damage and of other anti-ENA antibodies (anti-Scl-70 and/or anti-Jo-1) with premature gonadal failure. Other autoantibodies were not predictive of damage in individual organs.**
Conclusions. **Although autoantibodies are useful in diagnosis and predicting disease activity in SLE, they do not appear to be useful in predicting damage in SLE.**

Autoantibodies have been a hallmark of systemic lupus erythematosus (SLE). The presence of certain antibodies [antinuclear antibodies, anti-double-stranded DNA (anti-dsDNA) antibodies, anti-Sm antibodies and anti-phospholipid antibodies] has been used for diagnostic purposes [1]. Some of these antibodies have been linked to disease activity. Apart from this, the presence of certain antibodies has been associated with particular organ involvement in SLE, such as anti-dsDNA with lupus nephritis and anti-Ro with cutaneous lupus erythematosus.

The Systemic Lupus Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) is a validated instrument developed to measure irreversible damage in patients with SLE [2–4]. The damage may be a result of disease activity, its treatment or intercurrent illness.

The association between autoantibody profile in SLE with damage has not been well studied. Hence, the primary objective of this study was to determine if there is an association between the presence of autoantibodies and the occurrence of damage.

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Patients and methods

Patients

A prospective cohort of SLE patients attending Queen Elizabeth Hospital and City Hospital in Birmingham was set up by one of the authors (CG) in 1989. All patients satisfied the American College of Rheumatology criteria for SLE [1]. This study was approved by the local ethics committee and written consent was obtained from patients prior to inclusion in the study. During their follow-up, detailed clinical and serological information was recorded at each visit and entered into a specific lupus database [British Lupus Integrated Prospective System (BLIPS)] [5]. Damage was scored using SLICC/ACR DI every 6 months, and this index has been in use since 1993. The last SLICC/ACR score in the year 2000 or prior to death was used in this cross-sectional analysis. Disease duration was calculated from the time of diagnosis to the date of last assessment for SLICC/ACR DI.

Patients were excluded if they had been discharged from the clinic prior to 2000. Those who had died prior to 1993 and those who died with disease duration of less than 6 months would not have had a SLICC/ACR DI score, and these were also excluded.

Autoantibody assays

Anti-dsDNA antibodies were measured with an enzyme immunoassay (Bindazyme; The Binding Site Ltd, Birmingham, UK) kit. A patient was classified as being positive for anti-dsDNA antibody if they had ever had an anti-dsDNA antibody titre of more than 75 IU/ml.

Antibodies to extractable nuclear antigens (ENA) were screened using an enzyme immunoassay [Relisa (Immunoconcepts, Sacramento, CA, USA) ENA screen or Bindazyme ENA screen], which detects collectively autoantibodies against Ro, La, Sm, ribonucleoprotein (RNP), Scl-70 and Jo-1. Serum that was positive in this screen was then tested for autoantibodies against Ro, La, Sm, RNP, Scl-70 and Jo-1 with enzyme immunoassay (Relisa ENA or Bindazyme ENA). A result was considered positive when the titre was more than 25 IU/ml. Serum that was positive for anti-Scl-70 and/or anti-Jo-1 was classified as 'other ENA antibodies'.

Anti-cardiolipin (ACL) antibodies were measured with enzyme-linked immunosorbent assay (MELISA) or enzyme immunoassay (Bindazyme) kits. Tests for anti-cardiolipin IgG were considered positive when the titre was more than 11 U/ml, while for ACL IgM the cut-off for positivity was 10 U/ml.

Statistical analysis

Univariate analysis was performed with the χ^2 test, Fisher's exact test or univariate analysis of variance where appropriate. Multivariate analysis was performed using binary logistic regression. The model for multivariate analysis was tested for goodness of fit with the Hosmer and Lemeshow test. P values of less than 0.05 were considered statistically significant. Statistical calculations were done using SPSS for Windows version 10.0 (SPSS Inc., Chicago, IL, USA).

Results

There were 348 patients in this SLE cohort fulfilling the criteria for this analysis. The demographic characteristics of this cohort are shown in Table 1. There were 32 (9.2%) deaths within this cohort during the period of observation. One hundred and sixty-nine (48.6%) patients were positive for anti-dsDNA antibodies while 73 (21%) patients and 161 (46.3%) patients were positive for ACL and anti-ENA antibodies respectively (Table 2). One hundred and ninety-two patients (55.2%) did not have any damage recorded, indicated by a total SLICC/ACR DI score of 0, during follow-up of this cohort. The most common forms of organ system damage recorded were musculoskeletal, neuropsychiatric, cardiac and ocular. The distribution of damage according to organ system is demonstrated in Table 3.

Table 1. Demographic characteristics of SLE cohort ($n = 348$)

Age in years (yr): median (range)	40.9 (18.5–81.6)
Female sex: no. patients (%)	326 (93.7)
Race: no. patients (%)	
Caucasian	208 (59.8)
Afro-Caribbean	65 (18.7)
Asian	59 (17.0)
Oriental	4 (1.1)
Others	12 (3.4)
Disease duration (yr): median (range)	7 (1–43)

Table 2. Autoantibody profile of SLE cohort

Autoantibodies	*n* (%)
Anti-dsDNA	169 (48.6)
ACL	
Total	73 (21.0)
IgG	59 (17.0)
IgM	29 (8.3)
ENA	
Total	161 (46.3)
Anti-Ro	109 (31.3)
Anti-La	61 (17.5)
Anti-Sm	31 (8.9)
Anti-RNP	67 (19.3)
Others	35 (10.1)

Table 3. Distribution of damage according to organ system

Organ system or disease	No. of patients with score $\geqslant 1$ (%)	SLICC/ACR DI: median (range)
Total	156 (44.8)	0 (0–12)
Ocular	33 (9.4)	0 (0–2)
Neuropsychiatric	50 (14.4)	0 (0–4)
Renal	17 (4.9)	0 (0–3)
Pulmonary	27 (7.8)	0 (0–3)
Cardiac	35 (10.1)	0 (0–4)
Peripheral vascular	16 (4.6)	0 (0–4)
Gastrointestinal	15 (4.3)	0 (0–2)
Musculoskeletal	60 (17.2)	0 (0–4)
Skin	29 (8.3)	0 (0–2)
Premature gonadal failure	8 (2.3)	0 (0–1)
Diabetes mellitus	11 (3.2)	0 (0–1)
Malignancy	15 (4.3)	0 (0–2)

Predictors of damage

Race, sex, ACL antibodies, anti-Ro antibody, anti-La antibody, anti-Sm antibody, anti-RNP antibody and anti-dsDNA antibody were not significantly associated

with the presence of damage in univariate analysis. Only age, disease duration and other ENA antibodies (anti-Scl-70 and/or anti-Jo-1) were associated with the presence of damage (Table 4). Multivariate analysis revealed age ($P < 0.001$), disease duration ($P < 0.001$) and other ENA antibodies ($P = 0.029$) to be associated with damage.

Predictors of individual organ damage

Multivariate analysis with logistic regression revealed that the presence of damage in many organ systems was significantly associated with increasing age and longer disease duration. There was no association between damage in any organ system with ethnicity or sex. Autoantibodies did not appear to predict damage in any organ system apart from anti-Ro antibody for ocular damage and other ENA antibodies for premature gonadal failure (Table 5).

Discussion

There have been few studies done to date that look into predictors of damage in SLE. Most of these studies had drawbacks, such as retrospective assessment [6, 8], short disease duration [6, 10)] or the study being cross-sectional in design [7, 9] or having relatively small number of patients [8]. In this study, we report the results from a large cohort of SLE patients for whom data had been collected prospectively since 1989.

As expected, increasing age and disease duration were associated with damage that was in keeping with the results of previous studies [6–9]. However, we were not able to find any association between ethnicity and damage. Previous studies have revealed divergent results on the association between ethnicity and adverse outcomes; some show that Asians and Afro-Caribbeans are at greater risk [9, 14–16] while others do not [6, 13].

Although autoantibodies are useful in diagnosis and predicting disease activity in SLE, they do not appear to be predictive of damage. Even when individual organ damage was analysed, most autoantibodies were not significantly associated with damage of any individual organ. Only one previous cross-sectional study of Mexican patients with SLE has linked anti-dsDNA with damage [7].

A possible explanation for these differences is that current therapy is very effective in controlling disease activity and hence reducing the likelihood of damage directly related to disease. Furthermore, it has been shown in the Hopkins Lupus Cohort that the cumulative dose of corticosteroids is associated with osteoporosis, ischaemic heart disease and cataracts, while high-dose corticosteroid treatment (at least 60 mg prednisolone for at least 2 months) is significantly associated with avascular necrosis and stroke [11]. These items of damage are not directly due to active disease. Hence it is possible that most of the damage occurring in SLE patients is due to therapy rather than disease activity. At the moment, there is little data on the relationship between disease activity, treatment (steroids and immunosuppressive agents) and damage. This would require a prospective study on an inception cohort of lupus patients in which this information would be recorded regularly from within 1 yr of diagnosis.

TABLE 4. Univariate analysis of association of different characteristics with presence of damage

Characteristic	*P*
Age	< 0.001
Race	0.48
Sex	0.61
Disease duration	< 0.001
Anti-dsDNA antibody	0.046
Anti-Ro antibody	0.06
Anti-La antibody	0.45
Anti-Sm antibody	0.12
Anti-RNP antibody	0.10
Other ENA antibodies	0.003
ACL antibody	
All	0.16
IgG	0.31
IgM	0.70

TABLE 5. Multivariate analysis of associations between predictors and individual organ damage according to SLICC/ACD DI

Organ system damage	Predictor	*P*
Ocular	Age	< 0.001
	Anti-Ro	0.029
Neuropsychiatric	Disease duration	0.002
Renal	Disease duration	0.031
Pulmonary	Age	0.033
	Disease duration	0.034
Cardiac	Age	< 0.001
	Disease duration	0.028
Peripheral vascular	Age	0.019
Gastrointestinal	Disease duration	0.021
Musculoskeletal	Age	< 0.001
	Disease duration	0.040
Skin	Disease duration	0.003
Premature gonadal failure	Other ENA	0.031

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