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Peripheral Vascular Damage in Systemic Lupus Erythematosus: Data from LUMINA, a Large Multiethnic Cohort

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Summary

To determine the factors associated with peripheral vascular damage in systemic lupus erythematosus (SLE) patients and its impact on survival from LUMINA, a longitudinal multiethnic cohort. Peripheral vascular damage was defined by the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index (SDI). Factors associated with peripheral vascular damage were examined by univariable and multivariable logistic regression models and its impact on survival by a Cox multivariable regression. Thirty-four (5.3%) of 637 patients (90% women, mean [SD] age 36.5 [12.6] (16-87) years developed peripheral vascular damage. Age and the SDI (without peripheral vascular damage) were statistically significant (odds ratio [OR] =1.05, 95% confidence interval [CI] 1.01-1.08; p=0.0107 and OR=1.30, 95% CI 0.09-1.56; p=0.0043, respectively) in multivariable analyses. Azathioprine, warfarin and statins were also statistically significant, glucocorticoid use was borderline statistically significant (OR=1.03, 95% CI 0.10-1.06; p=0.0975). In the survival analysis, peripheral vascular damage was independenly associated with a diminished survival (Hazard Ratio =2.36; 95% CI 1.07-5.19; p=0.0334). In short, age was independently associated with peripheral vascular damage, but so was the presence of damage in others organs (ocular, neuropsychiatric, renal, cardiovascular, pulmonary, musculoskeletal and integument) and some medications (probably reflecting more severe disease). Peripheral vascular damage also negatively affected survival.

Introduction

The association between inflammatory rheumatic disease and atherosclerosis is well known. With the improvement of life expectancy in patients with systemic lupus erythematosus (SLE), atherosclerotic vascular events such as myocardial infarction, stroke, peripheral vascular disease and sudden death have been recognized as negatively impacting on their outcome [1,2]. However, to date the relationship between the factors associated with the occurrence of irreversible peripheral vascular damage and its impact on survival have not been explored in these patients.

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The presence of antiphospholipid antibodies, vasculitis and vasospasm may also contribute to the occurrence of peripheral vascular damage in SLE patients [3,4]. In addition, traditional atherosclerosis risk factors and comorbidities such as hypertension, insulin resistance (metabolic syndrome) and dyslipidemia may occur more frequently in lupus patients than in the general population.

We have now explored the factors associated with the occurrence of peripheral vascular damage as determined by SLICC (The Systemic Lupus International Collaborating Clinics) Damage Index or SDI [5] and its impact on survival on SLE patients from LUMINA, a multiethnic lupus cohort. We hypothesized that disease activity, damage in other organ systems and, particularly, traditional risk factors will be associated with the occurrence of peripheral vascular damage and that in turn peripheral vascular damage will contribute to these patients' decreased survival.

Patients and Methods

Patients

LUMINA (Lupus in Minorities, Nature versus nurture) is a longitudinal study of outcome in lupus [6]. All patients meet the American College of Rheumatology (ACR) criteria for the classification of SLE [7], have disease duration of ≤5 years, are ≥16 years of age, of defined ethnicity (African American, Hispanic [from Texas and Puerto Rico], or Caucasian), and live in the geographic recruitment area of the participating centers (the University of Alabama at Birmingham, the University of Texas Heath Science Center at Houston, and the University of Puerto Rico Medical Sciences Campus). The Institutional Review Board of these centers approved the study; written informed consent was obtained from each subject according to the Declaration of Helsinki.

Every patient had a baseline or enrollment visit (T0); follow up visits were conducted every 6 months during the first year (T0.5 and T1, respectively), and yearly thereafter. At each visit, the patients were interviewed, and physical examination and laboratory tests were performed. Data for missed study visits were obtained by review of all available medical records. Disease duration was defined as the time elapsing from the date the patients met four ACR diagnosis (TD) criteria for SLE to T0. Duration of followup was defined as the period between T0 and the last visit (TL).

Variables

As previously reported [8], the LUMINA database includes variables from the following domains: socioeconomic-demographic, clinical, immunologic, genetic, behavioral and psychological. These variables are measured at T0 and at every subsequent visit. Only the variables included in these analyses will be described.

Variables from the socioeconomic-demographic domain included were age, ethnicity, education, poverty (as defined by the US Federal government adjusted for the number of subjects in the household) [9] and smoking. Clinical variables included were disease duration, followup time, total disease duration, body mass index (BMI), disease activity and damage, disease manifestations (myocardial infarction, angina, heart failure, hypertension, cerebrovascular disease, diabetes, nephritis), laboratory variables, and medications.

Disease activity was assessed with the Systemic Lupus Activity Measure Revised (SLAM-R) [10] at T0 and at every visit; the average SLAM-R score for all visits (from TD to TL) was calculated as a measure of disease activity over time. Damage at T0 was measured with the SDI [5]. Peripheral vascular damage was removed from the SDI in these analyses. Peripheral vascular damage was defined per the corresponding domain of SDI: claudication, minor

tissue loss (pulp space), significant tissue loss ever (e.g. loss of digit or limb), venous thrombosis with residual swelling, ulceration or venous stasis, all present ≥six months [5].

The following laboratory variables were recorded at T0: low density lipoprotein (LDL), serum C-reactive protein (CPR) measured by high-sensitivity immunometric assay (hsCRP) (Immulite 2000 Diagnostic Products, Los Angeles, CA), and IgG and IgM antiphospholipid antibodies (aPL) (abnormal>13 IgG phospholipid units/ml, by enzyme-linked immunoabsorbent assay), and/or lupus anticoagulant (LAC) (Staclot test; Diagnostica Stago 92600, Asnieres-Sur-Seine, France). Cumulative exposure to glucocorticoids, hydroxychloroquine, cyclophosphamide, azathioprine, statins, low-dose aspirin, warfarin, low-molecular weight heparin and anti-platelet medications was also recorded.

Statistical analyses

Features from the different domains were compared between those patients who developed peripheral vascular damage and those who did not using Student's *t*-tests and Chi-square tests for continuous and categorical variables, respectively. Variables with $p \leq 0.10$ in these analyses were entered into multivariable logistic regression models to examine their independent association with peripheral vascular damage. Age, gender, and ethnicity were entered in all models. Two models were examined; in model one the medications were included while in model two they were omitted. The association between peripheral vascular damage and mortality was examined by a Cox multivariable regression, adjusting for variables previously found to be associated with mortality [age, gender, ethnicity, poverty and the damage index (without peripheral vascular damage)]. The level of statistical significance was set at $p \leq 0.05$; all statistical analyses were performed using the SAS software version 9.1 (SAS Institute, Cary, NC, USA).

Results

At the time of these analyses the cohort consisted of 637 patients; 90% of them were women with a mean (SD) age of 36.5 (12.6) (range 16-87) years; all ethnic groups were represented: Texan-Hispanic: 18%, Puerto Rican-Hispanic: 16%, African American: 37% and Caucasian: 28%. The mean (SD) disease duration and followup time were 1.5 (1.4) and 4.4 (3.4) years, respectively. Thirty-four (5.3%) patients (41 events) had developed peripheral vascular damage; four (8.5%) patients exhibited claudication, 19 (55%) minor tissue loss, seven (21%) significant tissue loss (one or two sites), and 11 (32%) venous thrombosis. Six the seven patients experiencing significant tissue loss, has lost a digit, and one had lost a foot, all presumably proceeding by gangrene. None of the seven patients lost a full limb or had a revascularization procedure performed prior to the amputations. Eleven (32%) patients had died as compared to 86 (14%) among those without peripheral vascular damage ($p=0.0043$).

Univariable Analyses

The distribution of damage in the different SDI domains is depicted in Table 1; ocular ($p=0.0076$), neuropsychiatric ($p=0.0071$), renal ($p=0.0230$), pulmonary ($p=0.0004$), cardiovascular ($p=0.0009$), musculoskeletal ($p<0.0001$), and integument ($p=0.0033$) occurred more frequently in those patients with peripheral vascular damage. Most of the variables known to be associated with atherosclerosis such as smoking, dyslipidemia, obesity and diabetes were similarly distributed among those patients who had developed peripheral vascular damage and those who had not. On the other hand hypertension, heart failure, and nephritis were more frequent in the peripheral vascular damage group but statistical significance was not reached for hypertension ($p=0.0758$; $p=0.023$; and $p=0.0081$, respectively). The use of warfarin did not substantially differed among patients who developed a venous thrombotic peripheral vascular damage event vs. those who did not

(46.2% vs 53.9%; x^2=0.95, p=0.3297); however its use was much higher than in those patients who had not developed a peripheral vascular damage event (35.3% vs 7.5%; x^2=36.03, p<0.0001); the use of statins was comparable among those with a presumed atherosclerotic peripheral vascular damage event (8.7%) vs. those without a presumed atherosclerotic event (9.1%) as well as in those patients who had not developed a peripheral vascular damage event (13.9%). The mean (SD) SLAM-R and SDI (excluding the peripheral vascular domain) scores were higher among those patients with peripheral vascular damage versus those without it [11.1 (4.3) and 3.5(2.7) vs. 8.0 (4.7) and 1.7 (2.0), respectively], but the differences were statistically significant only for the SDI (p=0.0001). The frequency of aPL antibodies was comparable among those patients who had developed peripheral vascular damage and those who had not [34.4% vs. 29.7% (x^2=0.31; p=0.5701) for IgM and /or IgG aPL antibodies and 13.0% vs. 9.1% for LAC (x^2=0.42; p=0.5103)].

Multivariable Analyses

The multivariable logistic regression models are depicted in Table 2. As expected, age and the SDI were significantly associated with peripheral vascular damage (OR=1.05, 95% CI 1.01-1.08, p=0.0107; and OR=1.30, 95% CI 0.09-1.56, p =0.0043, respectively) but so were azathioprine (OR=3.2, 95% CI 1.34-7.06; p =0.0087), warfarin (OR=6.16, 95% CI 2.43-15.59; p <0.0001); glucocorticoids were of borderline statistical significance (OR=1.03, 95% CI 0.10-1.06; p=0.0975) (model 1). On the other hand, statins were negatively associated with the occurrence of peripheral vascular damage (OR=0.20, 95% CI 0.05-0.80; p =0.0224);. The association with age and the SDI was confirmed in model 2.

In multivariable analyses, and after adjusting for pertinent variables, peripheral vascular damage was found to be a significant predictor of a diminished survival (HR=2.36; 95% CI 1.07-5.19; p=0.0334).

Discussion

The relationship between SLE and vascular events including cardiovascular, cerebrovascular and peripheral vascular has been well recognized [11] but no studies to date have focused on the factors associated with the development of peripheral vascular damage in these patients. We are now reporting that peripheral vascular damage occurs in older individuals and in the presence of damage in other organ systems. Furthermore, it seems that peripheral vascular damage has a negative impact on these patients' survival. Of importance, approximately fifty percent of our patients had peripheral vascular damage at the baseline visit or within a year and a half from disease onset, suggesting that involvement of the vascular system may occur early in SLE and that periodic surveillance of subclinical vascular disease in these patients is warranted; such early damage in the peripheral vascular system has not been observed by other investigators [12].

The prevalence of peripheral vascular damage in our cohort was 5.3% over nearly 6 years of disease duration and included both presumed atherosclerotic and thrombotic events; however, this distinction is not always clear and patients may had experienced both types of events. Albeit the contributing factors may be different depending on the type of event, more than one factor may be present concomitantly. These considerations, plus the relatively small number of individual peripheral vascular events our patients have had precluded us from performing further analyses. The contribution of the peripheral damage vascular domain to the total SDI score is variable; for instance, in a Mexican study involving 210 SLE patients, with a disease duration of nearly 12 years, peripheral vascular damage was reported in 10% of them [13], while in an Argentinean study (n=197) it occurred in 8.4 % of them at 10 years [14]; given the observation time in our study, our findings are consistent with those reported. Differences between studies may also relate to the number of patients studied

and their ethnic and geographic origin. Additionally, when peripheral vascular disease, rather than damage, had been examined, higher prevalence figures had been observed since subclinic vascular disease defined by Doppler abnormalities in the carotid and subclavia territories which will not be scored in the damage index are included [15].

As expected, we have observed significant damage in others organ system in patients with peripheral vascular damage; that has been the case for domains frequently associated with the development of accelerated atherosclerotic and vasculitis, but not with those primarily related to medication side effects (premature gonadal failure, diabetes and malignancy).

The association between age and peripheral vascular damage was predictable, given that endothelial injury from diverse sources tends to accumulate over time. Furthermore, age is an independent contributor to overall damage [16].

In terms of other variables explored, we were surprised about the lack of association between peripheral vascular damage and some variables that have been previously shown be associated with the occurrence of vascular events such as smoking, dyslipidemia, elevated C-reactive protein levels and antiphospholipid antibodies [11,17]. Furthermore, even though hypertension, lupus nephritis and, particularly, heart failure were significant in the univariable analyses, they were not retained in the multivariable models, perhaps because these other factors may impact damage overall which in turn was significantly associated with peripheral vascular damage. Furthermore, damage in general, suggests the presence of an ongoing inflammatory process which characterizes this disease. In term of the aPL antibodies, their lack of association with the occurrence of peripheral vascular damage probably reflects the fact that they were examined at entry into the cohort rather than closer to the time when the damage event occurred.

The association of peripheral vascular damage and medications should not be interpreted as causal but rather as reflecting a more severe disease (azathioprine) or as being used because of the presence of peripheral vascular damage (warfarin) or confounding by indication. The lower frequency of peripheral vascular damage among statin users may relate to their protective effect on the endothelium as postulated by Bruce [18]. Finally, although glucocorticoids have been associated with permanent damage, specially in some specific domains of the SDI (such as musculoskeletal, cardiovascular, ocular), we could not confirm the association with peripheral vascular damage perhaps suggesting their uneven effect on different vascular territories [12].

Peripheral vascular damage had a strong negative impact on survival which is not surprising given the SLE bimodal pattern of mortality as described by Urowitz *et al.* over 30 years ago, being the second peak related to atherosclerosis [2].

Even though our study includes a significant number of SLE patients with peripheral vascular damage (n=34), this number is still small; furthermore, given that about half of our cases had occurred before patients actually entered the cohort, we could not perform time-oriented analyses. In addition, the LUMINA protocol does not include data elements such as homocysteine levels, immune complexes and folic acid use, which could be important contributors or modulators of the outcome of interest [3].

In summary, even though peripheral vascular damage is infrequent, our analyses reveal that it occurs in older SLE patients and it is associated with the presence of damage in other organ systems. In addition, peripheral vascular damage is associated with a diminished survival confirming the bimodal pattern of mortality in SLE patients.

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Table. 1

Frequency distribution of the domains of the damage index according with the presence or absence of peripheral vascular damage.

Domains of the Damage Index n (%)	Peripheral Vascular Damage		*p* value*
	Yes n=34	No n=603	
Ocular	**11 (32.3)**	**91 (15.1)**	**0.0076**
Neuropsychiatric	**17 (50.0)**	**171 (28.4)**	**0.0071**
Renal	**12 (35.3)**	**116 (19.2)**	**0.0230**
Pulmonary	**8 (23.5)**	**41 (6.8)**	**0.0004**
Cardiovascular	**9 (26.4)**	**25 (4.1)**	**0.0009**
Gastrointestinal	3 (8.8)	34 (5.6)	0.1881
Musculoskeletal	**13 (38.2)**	**74 (12.3)**	**<0.0001**
Integument	**11 (32.3)**	**84 (13.9)**	**0.0033**
Premature gonadal failure	3 (8.8)	47 (7.8)	0.7433
Diabetes	2 (5.8)	43 (7.1)	1.0000
Malignancy	0 (0)	11 (1.8)	1.0000

* By the Chi-Square distribution

Table 2

Variables associated with peripheral vascular damage in LUMINA patients by multivariable logistic regression analyses.

	Model 1			Model 2		
Variable	**Odds Ratio**	**95% CI**	**p value**	**Odds Ratio**	**95% CI**	**p value***
Age	**1.05**	**1.01-1.08**	**0.0107**	**1.04**	**1.01-1.07**	**0.0217**
Gender	0.94	0.29-3.17	0.9178	0.88	0.29-2.71	0.8285
Ethnicity						
Hispanic-Texan	0.43	0.10-1.83	0.2546	0.43	0.11-1.64	0.2145
Hispanic-Puerto Rico			Reference Group			
African-American	0.42	0.12-1.51	0.1850	0.42	0.13-1.40	0.1583
Caucasian	0.30	0.07-1.30	0.1065	0.34	0.09-1.30	0.1156
CRP* High	1.07	0.41-2.80	0.8937	1.03	0.42-2.49	0.9564
CRP* Medium	0.57	0.20-1.70	0.3117	0.73	0.27-1.96	0.5275
CRP* Low			Reference Group			
Weighted Glucocorticoid	1.03	0.10-1.06	0.0975	1.03	0.99-1.05	0.0598
Damage Index†	**1.30**	**0.09-1.56**	**0.0043**	**1.30**	**1.17-1.52**	**0.0008**
Cardiac failure	1.82	0.63-5.25	0.2696	1.67	0.64-4.36	0.2940
Hypertension	1.07	0.40-2.89	0.8885	1.07	0.42-2.71	0.8854
Nephritis	2.18	0.77-6.17	0.1428	2.06	0.78-5.45	0.1445
Medications						
Azathioprine	**3.20**	**1.34-7.64**	**0.0087**			
Warfarin	**6.16**	**2.43-15.59**	**<.0001**			
Antiplatelets	3.11	0.60-16.22	0.1782			
Heparin	1.07	0.16-7.21	0.9483			
Statin	**0.20**	**0.05-0.80**	**0.0224**			
Aspirin (low dose)	0.55	0.18-1.62	0.2747			
Cyclophosphamide	0.65	0.25-1.70	0.3808			

*C reactive protein

†without peripheral vascular damage.