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Factors Associated with Arterial Vascular Events in PROFILE: A Multiethnic Lupus Cohort

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Summary

The objective of this study was to determine the factors associated with the occurrence of arterial vascular events in a multiethnic systemic lupus erythematosus (SLE) cohort. The PROFILE cohort, comprised of SLE patients (n=1,333) of defined ethnicity from five different U.S. institutions, was studied to determine demographic, clinical and biological variables associated with vascular events. An arterial vascular event (first episode) was either a myocardial infarction, angina pectoris and/or a vascular procedure for myocardial infarction, stroke, claudication and/or evidence of gangrene. Patient characteristics were analyzed by univariable and multivariable Cox proportional hazards regression analyses. One-hundred twenty-three (9.8%) patients had at least one incident arterial event. Age at cohort enrollment (HR= 1.04, 95% CI 1.03-1.06), smoking (HR= 2.20, 95% CI 1.40-3.46), and the *CRP2* C* alleles (HR= 1.91, 95%CI 1.04-3.49) were associated with a shorter time-to-the occurrence of arterial vascular events. Some clinical manifestations of disease activity were associated with a shorter time-to-occurrence [psychosis (HR= 2.21, 95% CI 1.10-4.44), seizures (HR= 1.85, 95% CI 1.00-3.24) and anemia (HR= 1.83, 95% CI 1.02-3.31)], but others were not [arthritis (HR= 0.32, 95% CI 0.18-0.58)]. In conclusion, older patients, especially in the context of a predisposing environmental factor (smoking) and severe clinical manifestations, are at higher risk of having arterial vascular events. The genetic contribution of the variation at the CRP locus was not obscured by demographic or clinical variables. Awareness of these factors should lead to more effective management strategies of patients at risk for arterial vascular events.

Introduction

There is strong evidence that systemic lupus erythematosus (SLE) patients have a markedly increased risk of cardiovascular disease (1-4) which is a major cause of late deaths among these patients (5-8). Hospitalizations due to cardiovascular disease are also more frequent among

lupus patients (9) and represent an important source of health-related expenditures among them.

Most studies of arterial vascular events, whether thrombotic or atherosclerotic in nature, have focused on their prevalence (10-14), their pathogenesis (15-23) or their socio-demographic features (4;8;10;11;24). We undertook this study to identify clinical and biological factors, including certain CRP gene polymorphisms, associated with arterial vascular events in PROFILE, a large multiethnic SLE cohort. We hypothesized that ethnic and genetic background, as well as specific clinical manifestations, would be associated with the occurrence of arterial vascular events. These data may be important in the identification of patients at high risk for such events, and may allow the design of preventive strategies which may beneficially impact on the morbidity and mortality associated with them in patients with SLE (10).

Patients and Methods

PROFILE is a multi-ethnic, multi-center prospective cohort of SLE patients (25). This cohort was constituted in 1998 by combining the existing cohorts at Northwestern University, Johns Hopkins University, the University of Alabama at Birmingham, the University of Texas Health Science Center at Houston, and the University of Puerto Rico. The Institutional Review Board of each institution approved this study and written informed consent was obtained from all participating subjects according to the Declaration of Helsinki.

PROFILE patients meet the American College of Rheumatology (ACR) revised and updated criteria (26;27), are 16 years of age or older, and have disease duration ≤ 10 years at the time they enter this cohort. They are of defined ethnicity [Hispanic of Mexican ancestry (residing and enrolled in Texas, hence Texan Hispanics), Hispanic of Puerto Rican ancestry (residing and enrolled in Puerto Rico, hence Puerto Rican Hispanics), African-American, and Caucasian], having reported all four grandparents to be of the same ethnic background. The PROFILE cohort includes patients from Northwestern University (N=175), Johns Hopkins University (N=528), The University of Alabama at Birmingham (N=299), The University of Texas Health Science Center at Houston (N=229), and The University of Puerto Rico (N=102).

Variables

The PROFILE database consists of variables common to the individual cohorts identified after carefully mapping the different cohorts' databases (25). Socioeconomic-demographic variables included age at cohort enrollment, gender and ethnicity. Clinical variables included current smoking status, hypertension (recording of three abnormal readings and/or the use of antihypertensive medications), cumulative SLE-related clinical manifestations from diagnosis to the time of the occurrence of an arterial vascular event, damage assessed at baseline by the Systemic Lupus International Collaborating Clinics Damage Index (SDI) (28). For these analyses, items included in the definition of arterial vascular events were excluded from the SDI. Lupus manifestations included were those described in the ACR classification criteria as well as selected clinical manifestations from the SDI domains. Antiphospholipid (aPL) antibodies including anticardiolipin IgM and IgG antibodies (by enzyme-linked immunosorbent assays) and/or the lupus anticoagulant (using activated partial thromboplastin time or Russel viper venom time assays), obtained at each site at study enrollment, and CRP gene alleles, which have been shown to associate with SLE, cardiovascular disease and CRP levels, were assayed or genotyped using standard laboratory techniques and appropriate primers as previously discussed (29-31). Cumulative exposure to glucocorticoids, hydroxychloroquine, cyclophosphamide, methotrexate, mycophenolate mofetil, azathioprine, and low dose aspirin were also examined.

Outcome variable—Consistent with the SDI, arterial vascular events were documented if myocardial infarction, angina pectoris and/or a vascular procedure for myocardial infarction (coronary artery bypass graft), cerebral vascular accident and claudication lasting $\geq$ six months and/or evidence of gangrene or significant tissue loss (loss of a digit or a limb) had occurred. Only the first incident event was examined. By definition, these events were recorded in the SDI only if 6 months had elapsed since the diagnosis of SLE had been made.

Statistical analyses

First, descriptive analyses were performed to compare the socio-demographic, clinical manifestations, immunologic and genetic features, disease damage and treatments received in patients with and without vascular events. The relationship between variables was examined by Student's *t* tests or Chi-square tests, as appropriate. Next, the association between variables and time-to-the occurrence of the first arterial vascular event (or events if two events occurred at the same time) was examined by univariable and multivariable analyses. First, univariable Cox proportional hazards regressions were examined, and all variables with a *p* value $\leq$ 0.10 in these analyses plus gender, ethnicity and disease duration at enrollment were then entered into a multivariable Cox proportional hazards regression model in which the dependent variable was time-to-the occurrence of arterial vascular events (prediction model). In an alternative (association) model, medications were included if $p \leq$ 0.10 in the univariable analyses. With the resultant hazard ratios (HR), a $HR \geq 1$ indicates a shorter time to event occurrence and a $HR < 1$ indicates a longer time-to-event occurrence. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, North Carolina, United States).

Results

One-thousand three hundred thirty-three patients were included in these analyses. As expected, patients were predominantly women (90.4%) with a mean age [mean (standard deviation, SD)] of 35.7 (12.3) years. All ethnic groups were represented, 139 (10.4%) were Texan Hispanics, 102 (7.7%) were Puerto Rican Hispanics, 472 (35.4 %) were African Americans, and 620 (46.5%) were Caucasians. The mean (SD) years of education of the PROFILE cohort was 13.7 (2.8) years, 88.5% had healthcare insurance and 61.6% were employed. Factors indicative of low socioeconomic status were more frequently seen for patients enrolled at the University of Texas Health Science Center at Houston; the mean (SD) years of education was 11.6 (3.2), 60.4% had health insurance, and 38.9% were employed. One-hundred seventeen (9.8%) patients had at least one arterial vascular event. Among these events, 29 were myocardial infarctions, 32 were angina pectoris and/or coronary artery bypass graft, 85 were strokes and 4 were peripheral artery disease; 19 patients had two events (stroke and MI or angina, $n=7$ and myocardial infarction and angina, $n=12$) whereas four patients had three events (stroke, myocardial infarction and claudication or angina), but, as already noted, only the first event was considered in these analyses.

Univariable analyses

Table 1 shows the socio-demographic features, cumulative clinical manifestations, genetic features, disease damage and pharmacologic treatments in patients with and without arterial vascular events. Patients with vascular events were older (42.3 ± 15.2 vs. 34.9 ± 11.8 , $p < 0.001$) and had longer disease duration at enrollment (2.9 ± 4.0 vs. 1.9 ± 3.2 , $p = 0.0007$) than those without vascular events. Patients with arterial vascular events were more likely ($p < 0.05$) to smoke cigarettes, to have discoid rash, valvular heart disease, hypertension, psychosis, seizures and anemia, and to receive treatment with intravenous glucocorticoids, azathioprine, cyclophosphamide and low-dose aspirin than patients without vascular events. In addition, patients with arterial vascular events had higher SDI scores (2.11 ± 2.50 vs. 1.08 ± 1.63 , $p < 0.001$).

Hazard ratios (HR) and 95% confidence intervals (95% CI) for the time-to-the-occurrence of arterial vascular events are depicted in Table 2. Neither female gender (HR=0.83, 95% CI 0.46-1.51) nor ethnicity (HR= 1.03, 95% CI 0.37-2.83 for Texan Hispanics; HR=1.04, 95% CI 0.44-2.45 for African Americans and HR=1.11, 95% CI 0.48-2.59 for Caucasians; Puerto Rican Hispanics was the reference group) were associated with time-to-the occurrence of arterial vascular events. Older age at cohort enrollment (HR=1.04, 95% CI 1.03-1.06) did have an association with a shorter time-to-the occurrence of arterial vascular events.

Hypertension (HR=2.07, 95% CI 1.39-3.09) and smoking (HR= 2.06, 95% CI 1.39-3.05) were associated with a shorter time-to-the occurrence of arterial vascular events, as were several other clinical characteristics [valvular heart disease (HR= 2.12, 95% CI 1.03-4.34), psychosis (HR= 2.76, 95% CI 1.60-4.74), seizures (HR= 1.93, 95% CI 1.19-3.11), anemia (regardless of type) (HR= 1.97, 95% CI 1.21-3.18)]. Other disease characteristics did not show an association [malar rash (HR=0.55, 95% CI 0.38-0.78) and arthritis (HR= 0.38, 95% CI 0.23-0.61)]. Interestingly, the presence of *CRP2***C* allele (rs1800947) was associated with a shorter time-to-the occurrence of arterial vascular events (HR = 1.75, 95% CI 1.00-3.07); other *CRP* alleles (*CRP4*, *CRP 409*, *CRP707*, *CRP821*, *CRP860*) were neither associated with a shorter nor with a longer time to the occurrence of arterial vascular events (data not shown). In terms of medications azathioprine (HR= 1.53, 95% CI 1.07-2.20) and low-dose aspirin (HR= 2.46, 95% CI 1.71-3.53) were associated with the occurrence of arterial vascular event while neither hydroxychloroquine nor glucocorticoids showed a relationship to their occurrence.

Multivariable analysis

Table 3 shows the results of the multivariable analysis with time-to-the occurrence of arterial vascular events as the dependent variable (prediction model). Smoking (HR= 2.20, 95% CI 1.40-3.46) remained a significant risk factor, but hypertension (HR=1.56, 95% CI 0.99-2.44) was of borderline statistical significance. *CRP2***C* alleles (HR= 1.91, 95% CI 1.04-3.49) also remained a significant risk factor as did some clinical manifestations, indicative of more severe disease. The results of the alternative regression (association model) were consistent with the model presented but low-dose aspirin was also retained (HR= 3.29, 95% CI 2.13-5.05) (data not shown).

Discussion

Arterial vascular events remain a common cause of morbidity and mortality among patients with SLE (3;4;6;7;32). Using the PROFILE database we have examined the risk factors for these events using a time-to-the event approach. In this cohort of 1333 SLE patients, we found that nearly 10% of patients developed at least one arterial vascular event over a median follow up time of 6.4 years. This proportion is similar to other reports from the United States (4;32) and Canada, (3) despite the fact that more than half of the patients in our study were of non-Caucasian ethnicity. We have also confirmed the association between arterial vascular events and age, cigarette smoking and certain clinical manifestations of disease severity. In addition, we have found the genetic variation in the *CRP* locus (rs1800947) linked with these arterial vascular events, an association not previously described for lupus patients.

Cigarette smoking, the most important preventable cause of premature death in the United States (33;34), was associated with a shorter time-to-the occurrence of arterial vascular events. In SLE, cigarette smoking has been identified both as a risk factor for the development of the disease (35) and as a disease modifier. For example, cigarette smoking has been associated with progression of lupus nephritis to end-stage renal disease (36) and with higher degrees of disease activity (37). More recently, it has also been recognized as a risk factor for both arterial (24;38;39) and venous thrombotic events (40) and as a modulator of the therapeutic response to antimalarial therapy (41;42), which has a protective effect against cardiovascular disease

(38). Cigarette smoking may contribute to these events through several different mechanisms including the formation of oxidized low density lipoprotein cholesterol, enhancement of a pro-thrombotic state, activation of the sympathetic nervous system and impaired prostacyclin production and endothelium-dependent vasodilation (43). A low-grade systemic inflammatory response occurs in chronic cigarette smokers (43;44) which may act synergistically with the chronic inflammatory process that characterizes SLE. Whatever the mechanism, smoking cessation is a mandatory prevention measure in lupus patients.

We have previously identified age as a risk factor for the development of venous thrombotic events and arterial vascular events in a subset of patients within the PROFILE cohort (40). Similarly, in a Canadian lupus cohort (11), patients with both arterial and venous thrombotic events were older than those patients who had not developed these events. Although the effect was modest in PROFILE, it is likely that risk factors for cardiovascular disease, as occur in the general population, continue to accrue throughout the lifespan giving a higher probability for their occurrence with age.

The fact that clinical manifestations of serious disease such as psychosis and seizures were associated with arterial events maybe an indicator that those patients with more active disease are at higher risk of suffering these events. Furthermore, both psychosis (45) and seizures (46) can be clinical manifestations of cerebral ischemia. They are also recognized neurological manifestations of the aPL syndrome (47), probably reflecting occlusion of the cerebral microvasculature. Anemia may compound this tendency (48) and reflect, in part, damage accrual which was also associated with a shorter time to the occurrence of arterial vascular events, even after excluding the items of the definition of arterial vascular events.

Several studies have now established that alleles within the *CRP* gene can influence CRP protein levels (30). The CRP gene consists of two exons and one intervening intron that contains a polymorphic GTⁿ repeat. Previously, we performed molecular typing of the CRP GTⁿ and found that the intron encoding 20 repeats (GT²⁰) was associated with arterial vascular events in SLE patients, particularly for African American and Hispanic patients (31). Also, the *CRP* promoter variants and the C allele of the synonymous SNP rs1800947 (*CRP2*) have been associated with basal CRP levels (30;49;50). Now, we are reporting the association of the C allele of the synonymous SNP rs1800947 (*CRP2*) with a shorter time to the occurrence of arterial vascular events. The lack of association with the promoter variant (including the variants associated with CRP levels, rs3093062 and the triallelic rs309244) may reflect statistical power given the minor allele frequencies. In general, the role of rs1800947 in cardiovascular disease is not well understood. Since CRP seems to be both a marker and a direct participant in cardiovascular disease, CRP genotypes associated with an increase on its synthesis may have an important role in the pathogenesis of atherosclerosis. However, rs1800947 is linked with decreased CRP promoter activity and hence, decreased levels of CRP (50). Despite this fact some studies have shown an association of rs1800947 with an elevated risk of cardiovascular disease, particularly in European-descent (51) and Japanese populations (52). Conversely, others have reported either no association with nonfatal myocardial infarctions and strokes (50), or a decreased prevalence of coronary artery disease; the latter in Mexican Americans (53). A study comparing this CRP polymorphism in lupus and non-lupus patients with arterial vascular events may help to elucidate if this allele confers a distinct risk to SLE patients.

Although it is entirely possible that medications may, to a certain extent, exert some effect in the occurrence of arterial vascular events, with hydroxychloroquine being protective (45) and being glucocorticoids detrimental (40), we could not include medications in our prediction model as the timing of their use is not uniformly available in all of the individual cohorts

constituting PROFILE. Thus the observed increased risk for low-dose aspirin should be interpreted as an associated occurrence and not as a predictor.

Unlike most studies on cardiovascular disease in SLE (10;13;15;16;54;55), we failed to demonstrate any significant association with aPL antibodies. One possible explanation for our results is that the assays used to test aPL antibodies were not homogenous across the constituent cohort centers; however, even when aPL antibodies were assessed longitudinally over time in the Hopkins cohort, this association could not be demonstrated. Similarly, although the HR for hypertension in the univariable analyses suggested a shorter time-to-the occurrence of arterial vascular events, this variable was not retained in the multivariable model. Nevertheless, the importance of hypertension as a risk factor for the occurrence of arterial vascular events should not be dismissed. Contributions of ethnicity, a variable also found to be a risk factor for cardiovascular disease, not only in lupus patients (10) but also in the general population (56; 57), were not evident in our model suggesting that smoking, certain clinical manifestations and *CRP* alleles convey strong associations.

We recognize that this study is not without some limitations. The fact that PROFILE is not a true inception cohort may have precluded identifying the predictors of their occurrence. We also recognize that complete assessment of disease activity, assessed over time, may be an important risk factor for arterial vascular events. Because disease activity was measured by different instruments in these cohorts, the possibility of examining all components of activity in all patients taken together was precluded. Similarly, previous smoking history and other important risk factors for arterial vascular events such as dyslipidemia (10), diabetes mellitus, and serial high-sensitivity C-reactive protein levels (24;40) were not available uniformly in all patients. Systematic evaluation of these factors and thrombophilic risk factors such as hyperhomocysteinemia (15;21;23), antiprothrombin antibodies (17;58) and other inherited and acquired thrombophilic conditions (59) is an important future goal. Nonetheless, we have identified important factors contributing to the development of arterial vascular events. Older patients, smokers, those with severe neurologic manifestations and those with a predisposing genetic background (alleles of the *CRP2* locus) are at higher risk for the occurrence of these events. Assessing the risk for arterial vascular events among lupus patients should be part of the routine clinical practice, and assessment of *CRP* genetics may be a useful adjunct to modification of environmental factors such as smoking cessation.

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Table 1

Socio-demographic Features, Cumulative Clinical Manifestations, Genetic Features, Disease Damage and Pharmacologic Treatments in PROFILE Patients with and without Arterial Vascular Events.

Variable	Arterial Vascular Events		<i>p</i> value
	Yes n=122	No n=1192	
Age at cohort enrollment, mean years (SD)	42.3(15.2)	34.9(11.8)	<0.001
Disease duration at enrollment, mean years (SD)	2.9(4.0)	1.9(3.2)	<0.001
Female gender, %	90.2	90.6	0.896
Ethnicity, %			

Variable	Arterial Vascular Events		<i>p</i> value
	Yes n=122	No n=1192	
Hispanics from Texas	8.1	10.8	
Hispanics from Puerto Rico	4.9	8.1	
African-American	35.8	35.4	
Caucasian	51.2	45.7	
Smoking, %	28.5	15.1	<0.001
Clinical manifestations, %			
Malar rash	48.8	57.7	0.057
Photosensitivity	65.9	64.6	0.781

0.39

Variable	Arterial Vascular Events		<i>p</i> value
	Yes n=122	No n=1192	
Subacute rash	3.3	3.4	0.913
Discoïd rash	24.4	16.6	0.030
Cutaneous vasculitis	8.9	10.2	0.671
Skin ulcers	4.1	1.6	0.066
Oral ulcers	57.7	59.0	0.788
Arthritis	83.7	86.7	0.106
Valvular heart disease	6.5	2.4	0.007
Hypertension	73.2	50.2	<0.001
Serositis	50.4	48.2	0.634
Transverse myelitis	0.8	0.3	0.325
Psychosis	12.5	3.6	<0.001
Seizures	16.3	7.7	0.001
Renal involvement	39.8	40.3	0.926
Anemia, any type	16.3	7.8	0.001
Lymphopenia	54.5	59.5	0.282
Thrombocytopenia	13.8	10.1	0.194
Antiphospholipid antibodies, %	39.8	34.0	0.193
CRP2GC, %	13.6	8.0	
CRP2GG, %	86.4	92.0	
SDI ^a , mean (SD)	2.11(2.50)	1.08(1.63)	<0.001
Treatments received, %			
Glucocorticoids, oral	90.2	84.7	0.096
Glucocorticoids, intravenous	40.7	25.3	0.003
Hydroxychloroquine	87.0	84.3	0.433
Azathioprine	39.0	24.2	<0.001
Mycophenolate mofetil	19.0	19.0	0.996
Methotrexate	22.0	15.3	0.054
Cyclophosphamide	28.5	20.0	0.027
Low-dose aspirin	56.9	26.3	<0.001

^aSystemic Lupus International Collaborating Clinics Damage Index

Table 2

Time-to-the-Occurrence of Arterial Vascular Events in PROFILE Patients by Univariable Cox Regression Analyses.

Feature	Hazard Ratio	95% Confidence Interval	p value
Age at cohort enrollment	1.04	1.03-1.06	<0.001
Female gender	0.83	0.46-1.51	0.540
Ethnicity ^a			
Hispanic from Texas	1.03	0.37-2.83	0.962
African-American	1.04	0.44-2.45	0.938
Caucasian	1.11	0.48-2.59	0.811
Disease duration at enrollment	0.97	0.92-1.01	0.138
Current smoking	2.06	1.39-3.05	<0.001
Clinical manifestations			
Malar rash	0.55	0.38-0.78	<0.001
Photosensitivity	0.84	0.58-1.22	0.364
Subacute rash	0.77	0.28-2.07	0.599
Discoid rash	1.25	0.83-1.89	0.294
Cutaneous vasculitis	0.65	0.35-1.21	0.649
Skin ulcer	1.73	0.70-4.25	0.233
Oral ulcer	0.82	0.57-1.17	0.264
Arthritis	0.38	0.23-0.61	<0.001
Valvular heart disease	2.12	1.03-4.34	0.040
Hypertension	2.07	1.39-3.09	<0.001
Serositis	0.87	0.61-1.25	0.456
Transverse myelitis	2.77	0.39-19.86	0.311
Psychosis	2.76	1.60-4.74	<0.001
Seizures	1.93	1.19-3.11	0.007
Renal involvement	0.83	0.58-1.20	0.324
Anemia, any type	1.97	1.21-3.18	0.006
Lymphopenia	0.88	0.62-1.27	0.513
Thrombocytopenia	1.03	0.62-1.72	0.912
Antiphospholipid antibodies	0.83	0.57-1.70	0.899
CRP2*C alleles ^b	1.75	1.00-3.07	0.051
SDI ^c	1.13	1.05-1.22	0.002
Treatments received			
Glucocorticoids, oral	1.33	0.73-2.42	0.348
Glucocorticoids, intravenous	1.44	0.99-1.07	0.051
Hydroxychloroquine	0.96	0.57-1.62	0.870
Azathioprine	1.53	1.07-2.20	0.021
Mycophenolate mofetil	0.87	0.55-1.39	0.566
Methotrexate	1.31	0.90-1.97	0.212
Cyclophosphamide	1.33	0.90-1.97	0.154

Feature	Hazard Ratio	95% Confidence Interval	p value
Low-dose aspirin	2.46	1.71-3.53	<0.001

^a Puerto Rican Hispanic is the reference group

^b GG is the reference group

^c Systemic Lupus International Collaborating Clinics Damage Index.

Table 3

Variables Independently Associated with Time-to-the-Occurrence of Arterial Vascular Events by Multivariable Cox Proportional Hazards Analysis.

Feature	Hazard Ratio	95% Confidence Interval	p value
Age at cohort enrollment	1.04	1.03-1.06	<0.001
Gender	1.36	0.65-2.84	0.412
Ethnicity ^a			
Texan Hispanic	0.73	0.24-2.44	0.582
African American	0.65	0.25-1.69	0.375
Caucasian	0.85	0.35-2.08	0.720
Disease duration at enrollment	0.95	0.90-1.00	0.057
Current smoking	2.20	1.40-3.46	<0.001
Hypertension	1.56	0.99-2.44	0.054
Malar rash	0.67	0.44-1.02	0.060
Arthritis	0.32	0.18-0.58	0.001
Valvular heart disease	1.41	0.54-3.68	0.483
Psychosis	2.21	1.18-4.44	0.026
Seizures	1.85	1.05-3.24	0.032
SDI ^b	1.10	1.00-1.22	0.051
Anemia	1.83	1.02-3.31	0.045
Antiphospholipid antibodies	1.00	0.64-1.55	0.989
CRP2* C alleles ^c	1.91	1.04-3.49	0.036

^a Puerto Rican Hispanic is the reference group

^b Systemic Lupus International Collaborating Clinics Damage Index

^c GG is the reference group.