Determinants of Risk for Venous and Arterial Thrombosis in Primary Antiphospholipid Syndrome and in Antiphospholipid Syndrome with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Antiphospholipid syndrome (APS) is characterized by thrombosis (venous and arterial) and pregnancy loss in conjunction with the lupus anticoagulant, IgG or IgM anticardiolipin, or IgG or IgM anti-ß$_2$-glycoprotein I. In most series, only a minority of patients with antiphospholipid antibodies develop a clinical manifestation.

Methods. A cross-sectional study of consecutive patients in the Hopkins Lupus Center was performed. Interviews were done and records were reviewed for the following variables: gender, ethnicity, hypertension, triglycerides, cholesterol, smoking, diabetes mellitus, homocysteine, cancer, hepatitis C, hormone replacement therapy/oral contraceptives, hereditary thrombophilia, anticardiolipin antibodies IgG, IgM and IgA, and lupus anticoagulant (LAC). Our aim was to identify risk factors associated with thrombosis and pregnancy loss in patients with antiphospholipid antibodies.

Results. A total of 122 patients (84% female, 74% Caucasian) were studied. Patients were divided into 3 groups: primary APS, APS associated with systemic lupus erythematosus, and patients with systemic lupus erythematosus (SLE) with antiphospholipid antibodies but no thrombosis or pregnancy loss. Venous thrombosis was associated with high triglycerides ($p = 0.001$), hereditary thrombophilia ($p = 0.02$), anticardiolipin antibodies IgG > 40 ($p = 0.04$), and LAC ($p = 0.012$). Hypertriglyceridemia was associated with a 6.4-fold increase, hereditary thrombophilia with a 7.3-fold increase, and anticardiolipin IgG > 40 GPL with a 2.8-fold increase in the risk of venous thrombosis. Arterial thrombosis was associated with hypertension ($p = 0.008$) and elevated homocysteine ($p = 0.044$). Hypertension was associated with a 2.4-fold increase in the risk of arterial thrombosis. No correlations were found for pregnancy loss.

Conclusion. The frequency of thrombosis and pregnancy loss is greater in APS associated with SLE than in primary APS. Risk factors differ for venous and arterial thrombosis in APS. Treatment of hypertension may be the most important intervention to reduce arterial thrombosis. Elevated triglycerides are a major associate of venous thrombosis, but the benefit of treatment is not known. Hereditary thrombophilia is an associate of venous but not arterial thrombosis, making it cost-effective to investigate only in venous thrombosis. (J Rheumatol First Release May 15 2009; doi:10.3899/jrheum.081194)

Key Indexing Terms:
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Antiphospholipid syndrome (APS) is a disorder characterized by vascular thrombosis and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPL)[1]. It is the most common cause of acquired hypercoagulability. The syndrome can be primary (PAPS) when occurring in patients without known autoimmune disease or associated with autoimmune diseases, particularly systemic lupus erythematosus (APS/SLE)[2].

Among patients with SLE who have the lupus anticoagulant (LAC), 50% will develop a venous thrombosis over a period of 20 years[3]. The "2 hit hypothesis" suggests that a second trigger may be needed for an asymptomatic patient with aPL to develop thrombotic complications and pregnancy morbidity.

Our aim was to identify potential associates and comorbid conditions that predispose to the development of thrombosis and pregnancy morbidity in individuals with aPL.

MATERIALS AND METHODS

Between January and July 2003, 122 patients with aPL were consecutively enrolled in the study. Informed consent was obtained. Patients were interviewed and a retrospective chart review was undertaken. The following factors were examined to determine their influence on thrombosis risk: ethnicity, gender, hypertension, diabetes mellitus, cancer, family history of thrombosis, smoking, thrombophilia (deficiency of protein C, S, antithrombin III, and factor V Leiden mutation), hyperhomocysteinemia, high cholesterol, high triglycerides, hepatitis C, oral contraceptive pills (OCP), and hormone replacement therapy (HRT).

Deep venous thrombosis was defined by ultrasound and pulmonary embolus by ventilation/perfusion scan or spiral computerized tomography (CT). Arterial thrombosis, if stroke, was defined by brain magnetic resonance imaging (MRI) or CT, and if myocardial infarction, by appropriate electrocardiographic changes, CK or troponin change, or cardiac imaging. Other arterial thrombosis was defined as appropriate for the site involved.

Laboratory testing. Anticardiolipin IgG, IgM, and IgA antibodies were determined by ELISA (Inova) and were considered high positive if > 40 IU. LAC was determined by the modified dilute Russell's Viper Venom Time test (dRVVT), with confirmatory mixing studies. Arterial thrombosis, venous thrombosis, and pregnancy loss were defined according to the International Criteria for Antiphospholipid Syndrome[4].

Statistical analysis. The associations between clinical events and risk factors were examined using contingency table analysis and chi-square and Fisher's exact test. Logistic regression was performed with APS-related events as the dependent variable. Statistical significance was set at 0.05.

RESULTS

Of 122 patients enrolled, 102 (84%) were female and 20 (16%) male. The majority of patients were Caucasian (91, 75%), 29 (24%) were African American, and 2 (1%) Asian. Patients were classified as having PAPS (17, 14%), APS/SLE (59, 48%), and SLE/aPL (46, 35%). The last group served as a control group because the patients had no history of thrombosis, recurrent miscarriage, or late fetal death.

Demographic variables, risk factors, and comorbidities are compared in Table 1. Arterial thrombosis was present in 39 patients, venous thrombosis in 46, and fetal loss in 39 patients (Figure 1).

LAC was present in all patients with PAPS, 97% of patients with SLE associated APS (APS/SLE), and 76% of patients with SLE/aPL. Anticardiolipin IgG was present in 71% of patients with PAPS, 37% of patients with APS/SLE, and 44% of patients with SLE/aPL. Anticardiolipin IgM was present in 47% of patients with PAPS, 31% of patients with APS/SLE, and 46% of patients with SLE/aPL. Anticardiolipin IgA was present in 14% of patients with PAPS, 8.5% of patients with APS/SLE, and 8.9% of patients with SLE/aPL.

Table 2 shows the results of analyses of risk factors for arterial thrombosis. Arterial thrombosis was associated with hypertension (p = 0.008), hyperhomocysteinemia (p = 0.044), and OCP/HRT (p = 0.036). Only hypertension remained as an independent risk for arterial thrombosis in a logistic regression model (Table 3). Diabetes mellitus was more frequent among patients who had arterial thrombosis, but this finding did not reach statistical significance.

Table 4 shows the univariate analyses of variables potentially associated with venous thrombosis. Venous thrombosis was associated with hypertriglyceridemia (p = 0.001), hereditary hypercoagulable states (p = 0.02), anticardiolipin IgG > 40 GPL (p = 0.04), and LAC (p = 0.012). In the multivariate analysis, hypertriglyceridemia, hereditary thrombophilia, and anticardiolipin IgG > 40 were independent associates of venous thrombosis (Table 5).

Analysis of potential risk associates of fetal loss failed to identify any statistically significant association. The frequencies of risk factors were similar for those with and without pregnancy morbidity (Table 6).

Table 1. Demographic features, risk factors, and comorbidities in the study population. Data are number (%).

Characteristic	Primary APS, n = 17	Secondary APS/SLE, n = 59	SLE/aPL, n = 46	p (APS vs SLE/+aPL)
Female	13 (76)	49 (83)	40 (87)	0.43
Caucasian	16 (94)	44 (73)	31 (67)	0.21
Family history	1 (6)	1 (2)	0	0.52
Smoking	3 (17)	8 (13)	5 (11)	0.56
Diabetes mellitus	1 (6)	4 (7)	1 (2)	0.4
Malignancy	1 (6)	7 (12)	5 (11)	1
Hypertension	6 (35)	29 (49)	13 (28)	0.051
Hereditary thrombophilia*	2 (12)	8 (13)	1 (2)	0.051
Hyperhomocysteinemia††	3 (25)	28 (49)	12 (27)	0.049
Hypercholesterolemia	7 (41)	22 (37)	14 (30)	0.38
Hypertriglyceridemia**	4 (36)	14 (24)	2 (5)	0.005
Hepatitis C†	0	2 (9.5)	0	0.51
OCP/HRT	1 (5.9)	5 (8.5)	8 (17)	0.11

* Data available for 55 patients; ** data available for 111 patients; † data available for 42 patients; †† data available for 114 patients. OCP/HRT: oral contraceptive pill/hormone replacement therapy; APS: antiphospholipid syndrome; APS/SLE: APS with associated systemic lupus erythematosus; aPL: antiphospholipid antibodies.

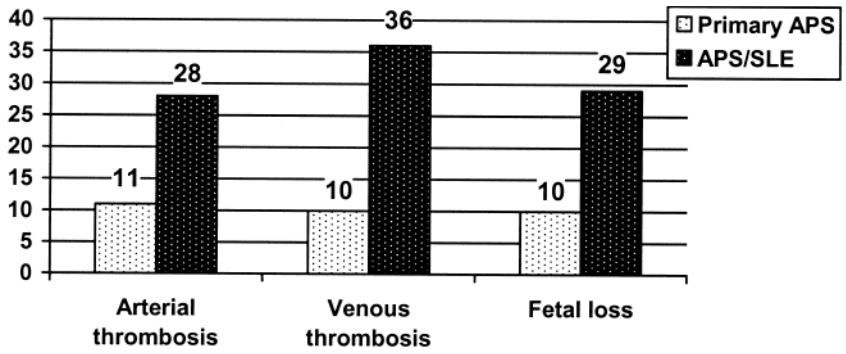

Figure 1. Prevalence of arterial thrombosis, venous thrombosis, and fetal loss in primary and secondary antiphospholipid syndrome.

Table 2. Arterial thrombosis: univariate analysis.

Variables	Available Data	Missing Data	p
Ethnicity	122	0	0.32
Sex	122	0	0.17
Malignancy	122	0	0.75
Smoking	122	0	0.94
Diabetes mellitus	122	0	0.082
Hypertension	122	0	0.008
Hyperhomocysteinemia	114	8	0.044
Hypercholesterolemia	122	0	0.91
Hypertriglyceridemia	111	11	0.78
Hereditary thrombophilia	55	67	1
OCP/HRT	122	0	0.036
aCL IgG	122	0	0.77
aCL IgG > 40	122	0	0.62
aCL IgM	122	0	0.22
aCL IgA	119	3	0.74
Lupus anticoagulant	121	1	0.22

OCP/HRT: oral contraceptive pill/hormone replacement therapy; aCL: anticardiolipin antibody.

Table 3. Arterial thrombosis: logistic regression model.

Variables	Odds Ratio (95% CI)	p
Diabetes mellitus	3.38 (0.54–20.80)	0.18
Hypertension	2.45 (0.98–6.09)	0.053
Hyperhomocysteinemia	1.42 (0.55–3.64)	0.46
Gender	0.95 (0.30–2.96)	0.93
OCP/HRT	0.18 (0.02–1.53)	0.11

OCP/HRT: oral contraceptive pill/hormone replacement therapy.

DISCUSSION

Previous studies suggested that factors predictive of thrombosis in aPL–positive patients are the LAC[5-7], high-titer IgG anticardiolipin[8,9], and persistence of the aPL antibodies over time[10]. We were able to assess multiple risk factors — both acquired and genetic — in a large sample of patients with a large number of thrombotic events. We found that the LAC and high-titer IgG anticardiolipin were both significant associates of venous thrombosis in univariate analyses. Although it might seem surprising that OCP/HRT was not associated with venous thrombosis, this is likely because exogenous estrogen was almost never prescribed to patients with SLE or APS.

The strong association of hypertriglyceridemia with venous thrombosis is not understood. However, 2 studies of patients with idiopathic venous thrombosis confirmed this finding[11,12]. It is possible that an effect of triglycerides on endothelial cells expressing plasminogen activator inhibitor

Table 4. Venous thrombosis: univariate analysis.

Variable	Valid	Missing	p
Ethnicity	122	0	0.65
Sex	122	0	0.81
Malignancy	122	0	0.55
Smoking	122	0	0.56
Diabetes mellitus	122	0	0.4
Hypertension	122	0	0.46
Hyperhomocysteinemia	114	8	0.23
Hypercholesterolemia	122	0	0.48
Hypertriglyceridemia	111	11	0.001
Hereditary thrombophilia	55	67	0.02
OCP/HRT	122	0	0.45
aCL IgG	122	0	0.53
aCL IgG > 40	122	0	0.04
aCL IgM	122	0	0.83
aCL IgA	119	3	1
Lupus anticoagulant	121	1	0.012

OCP/HRT: oral contraceptive pill/hormone replacement therapy; aCL: anticardiolipin antibody.

Table 5. Venous thrombosis: logistic regression model.

Variables	Odds Ratio (95% CI)	p
Hypertriglyceridemia	6.38 (2.05–19.83)	0.001
Hereditary thrombophilia	7.34 (1.54–34.96)	0.012
aCL anticardiolipin IgG > 40	2.77 (1.07–7.17)	0.035
Lupus anticoagulant	5.38 (0.6–47.56)	0.13

Table 6. Pregnancy loss (one or more miscarriages or late fetal loss): univariate analysis.

Variable	Available Data	Missing Data	Patients with Fetal Loss, n (%), total 48	Patients with No Fetal Loss, n (%), total 54	p
Malignancy	102	0	8 (15)	3 (6)	0.16
Smoking	102	0	7 (15)	7 (13)	0.81
Family history	102	0	1 (2)	0	*
Diabetes mellitus	102	0	3 (6)	1 (2)	0.34
Hypertension	102	0	18 (37)	19 (35)	0.8
Hyperhomocysteinemia	96	6	13 (29)	18 (35)	0.5
Hypercholesterolemia	102	0	15 (31)	19 (35)	0.67
Hypertriglyceridemia	93	9	10 (23)	7 (14)	0.29
Hepatitis C	35	67	2 (12)	0	*
Hereditary thrombophilia	45	57	6 (12)	2 (4)	0.14
aCL IgG > 40	102	0	16 (33)	16 (30)	0.68
aCL IgG	102	0	19 (40)	27 (50)	0.29
aCL IgM	102	0	19 (40)	21 (39)	0.94
aCL IgA	100	2	3 (6)	6 (11)	0.5
Lupus anticoagulant	101	1	43 (91)	45 (83)	0.22

* Not possible to perform statistical tests.

or resistance to activated protein C is involved[11,12]. Hereditary thrombophilia does appear to be a "second hit" for venous thrombosis in our study. The G20210A mutation was associated with venous thrombosis in one study of patients with SLE[13].

Hypertension was by far the strongest associate of arterial thrombosis. Homocysteine was also significantly associated in univariate analyses. Elevated concentrations of homocysteine are common in SLE and are predictive of later stroke and arterial thrombosis[14]. Homocysteine was not an independent predictor, however, in the logistic regression model. A similar finding has been reported by Martinez, *et al*[15]. Indeed, it is controversial whether homocysteine is the direct cause of cardiovascular morbidity, in that intervention trials to reduce homocysteine have not reduced later cardiovascular events[16,17].

Surprisingly, no associates of pregnancy loss were found. In the general population and some APS studies, hereditary thrombophilia and homocysteine are associated with pregnancy loss[18-21].

We show that the frequency of thrombosis and pregnancy loss is greater in APS associated with SLE than in primary APS (Figure 1). This is not surprising given the additional traditional cardiovascular risk factors, such as hypertension, that accrue in SLE, and potentially lupus-associated endothelial activation and damage. It suggests the strong rationale for prophylactic, preventive therapy in SLE patients with aPL. This was underscored in our previous prospective analysis of the Hopkins Lupus Cohort, in which, 20 years after diagnosis, 50% of SLE patients with the LAC had had a venous thrombotic event[3].

In summary, there are "second hits" for arterial and venous thrombosis in antiphospholipid-positive patients. Two factors, hypertension for arterial thrombosis and hypertriglyceridemia for venous thrombosis, are amenable to modification. Future studies, prospective rather than cross-sectional in design, are needed to confirm our findings.

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