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Risk factors for a first thrombotic event in antiphospholipid antibody carriers: a prospective multicentre follow-up study.

Amelia Ruffatti[1], Teresa Del Ross[1], Manuela Ciprian[1], Maria T Bertero[2], Sciascia Salvatore[2], Salvatore Scarpato[3], Carlomaurizio Montecucco[4], Silvia Rossi[4], Paola Caramaschi[5], Domenico Biasi[5], Andrea Doria[1], Mariaelisa Rampudda[1], Nuzzo Monica[6], Fabio Fischetti[7], Ugo Picillo[8], Antonio Brucato[9], Elisa Salvan[1], Pengo Vittorio[10], Pierluigi Meroni[11], Angela Tincani[6], Antiphospholipid Syndrome Study Group of the Italian Society of Rheumatology.

[1]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Padua, Padua, Italy

[2]Clinical Immunology and Allergology Units, Mauriziano Hospital, Turin, Italy

[3]Rheumatology Unit, M Scarlato Hospital, Salerno, Italy

[4]Rheumatology Unit, IRCCS Policlinico S Matteo Foundation, University of Pavia, Pavia, Italy

[5]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Verona, Verona, Italy

[6]Rheumatology and Clinical Immunology Unit, University of Brescia, Brescia, Italy

[7]Department of Medical, Technological and Translational Sciences, University of Trieste, Trieste, Italy

[8]Rheumatology Unit, Department of Internal Medicine, 2nd University of Naples, Naples, Italy

[9]Department of Internal Medicine, Hospital of Bergamo, Bergamo, Italy

[10]Clinical Cardiology, Thrombosis Centre, University of Padua, Padua, Italy

[11]Department of Internal Medicine, Auxologico Institute, University of Milan, Milan, Italy

Abstract

Objectives To assess risk factors for a first thrombotic event in confirmed antiphospholipid (aPL) antibody carriers and to evaluate the efficacy of prophylactic treatments.

Methods Inclusion criteria were age 18–65 years, no history of thrombosis and two consecutive positive aPL results. Demographic, laboratory and clinical parameters were collected at enrolment, once a year during the follow-up and at the time of the thrombotic event, whenever that occurred.

Results 258 subjects were prospectively observed between October 2004 and October 2008. The mean±SD follow-up was 35.0±11.9 months (range 1–48). A first thrombotic event (9 venous, 4 arterial and 1 transient ischaemic attack) occurred in 14 subjects (5.4%, annual incidence rate 1.86%). Hypertension and lupus anticoagulant (LA) were significantly predictive of thrombosis (both at $p<0.05$) and thromboprophylaxis was significantly protective during high-risk periods ($p<0.05$) according to univariate analysis. Hypertension and LA were identified by multivariate logistic regression analysis as independent risk factors for thrombosis (HR 3.8, 95% CI 1.3 to 11.1, $p<0.05$, and HR 3.9, 95% CI 1.1 to 14, $p<0.05$, respectively).

Conclusions Hypertension and LA are independent risk factors for thrombosis in aPL carriers. Thromboprophylaxis in these subjects should probably be limited to high-risk situations.

Introduction

It is unclear if persistent antiphospholipid (aPL) antibodies in the blood are a risk factor for a first thrombotic event, and consequently guidelines have yet to be established regarding antithrombotic prophylaxis in these subjects. Retrospective,[1-4] case–control[5–12] and cross-sectional[13, 14] studies with different designs, patient selection criteria, aPL profiles and risk factors have produced contradictory results. We recently conducted a large retrospective study[15] exclusively focused on carriers with confirmed aPL positivity. Our results showed that hypertension and

medium/high titres of IgG anticardiolipin antibodies (aCL) are independent predictors of thrombosis. Long-term thromboprophylaxis management and management during high-risk periods were, moreover, found to be independent protective factors against thrombosis only when considered together but, when analysed separately, none was protective against thrombosis.

Some prospective studies have likewise failed to produce reliable results since patients with vascular antiphospholipid syndrome (APS) and carriers of aPL were considered together.[16–18] The aim of the present study was to assess risk factors for a first thrombotic event in aPL carriers with at least two consecutive positive test results no less than 12 weeks apart, and to evaluate the efficacy of primary prophylactic treatments.

Methods

Study population

The study concentrated on aPL carriers attending 11 rheumatology centres, all belonging to the APS Study Group of the Italian Society of Rheumatology network. The study population was selected from subjects tested for aPL for one or more of the following reasons: previous pregnancy morbidity, systemic lupus erythematosus (SLE) or other autoimmune diseases, familiar aPL or APS, before starting oral contraceptive or hormone replacement therapy, prolonged activated partial thromboplastin time and biologically false-positive tests for syphilis. The clinical inclusion criteria were age 18–65 years and no history of any type of vascular thrombosis. Laboratory criteria for inclusion were at least two consecutive positive results for the same aPL antibody(ies) including lupus anticoagulants (LAs) and/or IgG/IgM aCL and/or IgG/IgM anti-β2-glycoprotein I (anti-β2GPI) carried out no less than 12 weeks apart.[19] Women with APS-related pregnancy morbidity, classified in accordance with the Sydney classification criteria for APS,[19] were also included. Ninety-seven patients participating in the retrospective study15 were also enrolled in the current one. Clinical and laboratory parameters (tables 1 and 2) were collected at enrolment and once a year during the follow-up period and whenever a thrombotic event occurred.

The type of prophylactic treatment employed, such as long-term (ie, continuous use of) low-dose aspirin (LDA, 100 mg), long-term warfarin or LDA ± heparin administered during high-risk periods (pregnancy/puerperium, immobilisation and surgery), was recorded. Long-term LDA was initiated arbitrarily for the following reasons: SLE or other autoimmune diseases, obstetric APS, thrombocytosis and LA positivity. Warfarin was administered as prophylactic treatment for high-risk conditions such as pulmonary hypertension in connective tissue diseases. Drug compliance was monitored on the basis of self-reports by participants. The number of patients who withdrew and the side effects of prophylactic treatment were also registered. Subjects were withdrawn from the study when a vascular thrombosis, defined in accordance with the last consensus paper,[19] took place. In accordance with the Sydney Consensus Conference Criteria,[19] transient ischaemic attacks (TIAs) were considered falling ‘within the spectrum of thrombosis’.

aPL detection

aCL and anti-β2GPI of IgG and IgM isotypes were determined in five centres by home-made ELISA procedures. In accordance with the Sydney update of the classification criteria for APS,[19]the cut-off values for medium/high titres for aCL as well as for anti-β2GPI antibodies were calculated using the 99th percentile obtained by testing age-matched healthy subjects. These ranged between 6.2 and 21.0 immunoglobulin G phospholipid units (GPL) for IgG aCL, between 17.4 and 21.0 immunoglobulin M phospholipid units (MPL) for IgM aCL, between 2.1 and 12.1 Units for IgG anti-β2GPI, and between 8.5 and 13.9 Units for IgM anti-β2GPI antibodies. The other six centres assessed IgG/IgM aCL and IgG/IgM anti-β2GPI antibodies using commercial kits following the manufacturers' instructions. The cut-off values for medium/high titres ranged between 10 and 40 GPL for IgG aCL, between 10 and 40 MPL for IgM aCL, between 10 and 20 Units for IgG anti-β2GPI, and between 10 and 20 Units for IgM anti-β2GPI antibodies. LA was determined by multiple coagulation tests using platelet-poor plasma samples following internationally accepted guidelines.[20]

Statistical analyses

Univariate analysis was performed to assess the association between thrombotic events and risk factors using the Pearson, χ^2 and Fisher exact tests. A Kaplan–Meier survival analysis and the log-rank test were carried out to analyse the cumulative incidence of events in the groups of patients with and without potential risk factors. The McNemar test was employed in the patients who developed thrombosis to evaluate if there was a significant difference between the distribution of risk factors found at the time of enrolment and at the time of the thrombotic event. Multivariate survival analysis was performed using the proportional hazards model (Cox model) to identify significant independent factors adjusted for the potential confounding risk factors able to predict a thrombotic event. The forward conditional techniques were used to find the final model. The results are expressed as HRs with 95% CI.

Results

A cohort of 258 Caucasian confirmed aPL carriers (223 women and 35 men, mean±SD age 40.9±11.1 years, range 18–65) without a history of thrombosis were prospectively evaluated between 15 October 2004 and 15 October 2008 for a mean±SD follow-up of 35.0±11.9 months (range 1–48). Their baseline clinical characteristics and risk factors for thrombosis as well as the prophylactic treatments are shown in table 1. High-risk situations (surgery/immobilisation, pregnancy/puerperium) occurring during the follow-up period are also specified. Although none of the participants developed serious adverse events such as major bleeding episodes during prophylaxis, three patients discontinued long-term prophylaxis for personal reasons. Forty-nine of the patients presented with pregnancy morbidity at enrolment and four presented with pregnancy morbidity during the follow-up; aPLs were detected in all of these women at the time the diagnosis was formulated and then, according to the study protocol, once a year. Twenty-nine (54.7%) of the 53 women with obstetric APS took LDA prophylaxis continuously, beginning at the presentation of pregnancy morbidity. The results of the baseline autoantibody assays are shown in table 2. During the follow-up period 189 subjects (73.3%) maintained at least one aPL antibody at medium/high titre while 69 (26.7%) became negative or positive to a different antibody.

First thrombotic event

Fourteen patients (5.4% of the study population; 10 women and 4 men with a mean±SD age of 39.9±11.7 years, range 23–60) had a first thrombotic event (9 venous thromboses (64.3%), 4 arterial thromboses (28.6%), 1 TIA (7.1%)) after a mean±SD follow-up of 21.4±18.3 months (range 1–47.6). The thrombosis incidence rate was 1.86 per 100 patients per year. The clinical and laboratory features of these patients at baseline and at the time of the thrombotic event are shown in tables S1 and S2 in the online supplement. Clinical and laboratory profiles (including risk factors for thrombosis) at the time of the thrombotic event were not significantly different from those recorded at baseline.

Analysis of risk factors for thrombosis

All demographic, clinical and laboratory characteristics, including risk factors for thrombosis, were evaluated by univariate analysis (tables 1 and 2). Hypertension and LA were significantly associated with thrombosis (both $p<0.05$). As shown in figure 1, Kaplan–Meier survival analysis provided similar results: the cumulative incidence of thromboembolic events was significantly higher in patients with hypertension ($p<0.01$) and LA ($p<0.05$). Finally, analysis of the relationship between each variable (hypertension, medium/high IgG aCL levels and prophylaxis) and venous/arterial thrombosis or TIA, considered separately, uncovered no significant association.

Thromboembolic events were significantly reduced only when antithrombotic prophylaxis was administered in high-risk situations (OR 0.1, 95% CI 0.01 to 0.9, $p<0.05$). Continuous prophylaxis was not associated with a reduction in thromboembolic events.

Multivariate analysis adjusted for potential confounding risk factors such as age, sex, aPL antibodies, hypertension, autoimmune diseases, pregnancy/puerperium, smoking, hypercholesterolaemia, body mass index, pill/hormone replacement therapy or diabetes

mellitus indicated that only hypertension (HR 3.8, 95% CI 1.3 to 11.1, p<0.05) and LA (HR 3.9, 95% CI 1.1 to 14, p<0.05) were independent risk factors for thrombosis.

Discussion

The most important finding of this study is that hypertension and LA positivity are two independent risk factors for thrombosis in aPL carriers.

The finding that hypertension is a risk factor for thrombosis is not a novel one as we reported this in our previous retrospective study on aPL carriers.[15] An association between hypertension and arterial thrombosis was also reported by one cross-sectional[13] and one prospective study17 aiming to identify the predictors of vascular events in cohorts of both APS patients and aPL carriers. Nor is LA positivity a novel risk factor for thrombosis, as three case–control studies on aPL carriers[5,6,12] reported that it is associated with arterial and/or venous thrombosis. The present work is different from the others because it is the first prospective study focusing on an entirely homogeneous cohort including only confirmed aPL carriers without a history of thrombosis who underwent three antibody tests (LA, aCL and anti-β2GPI antibodies). In agreement with previously reported findings,[1,15] pregnancy was not associated with thrombosis in our patients. This is probably due to the fact that most of the pregnant women being studied here were protected by LDA ± low molecular weight heparin prophylactic treatment.

In accordance with international guidelines, all participating centres strongly advised aPL carriers to avoid taking contraceptive pills or hormone replacement therapy. As a consequence, the small number of women studied here taking those drugs probably explains why no association was found with thrombotic events.

Finally, the number of thrombotic events was rather low (incidence rate 1.86% per 100 patients per year) and similar to that reported in other studies[1–3,7,8,13,16] and by our own retrospective study.[15] Primary prophylaxis in high-risk situations was found to be a significant protective factor against thrombosis according to univariate analysis. Similar results were obtained in a prospective study17 which reported no thrombotic events in 178 aPL carriers using thromboprophylaxis in high-risk situations.

We can therefore conclude that hypertension and LA were independent risk factors for thrombosis in this prospective cohort study on confirmed aPL carriers with no history of thrombosis. Thromboprophylaxis should probably be limited in these patients to high-risk situations. The fact that there was no central laboratory for aPL testing, which certainly represents a missed opportunity, and the short follow-up period can be considered limitations of the study. Long-term prospective studies using a central reference laboratory for all the participating centres are warranted.

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Table 1

Baseline clinical characteristics of antiphospholipid carriers, prophylaxis and the thrombosis rate in the study subjects

		Thrombotic events	
Clinical characteristics	**Prevalence**	**No**	**Yes**
Systemic autoimmune diseases	177/258 (68.6%)	167/244 (68.4%)	10/14 (71.4%)
Systemic lupus erythematosus	70/258 (27.1%)	66/244 (27.0%)	4/14 (28.6%)
Others *	107/258 (41.5%)	101/244 (41.4%)	6/14 (42.9%)

Clinical characteristics	Prevalence	Thrombotic events	
		No	Yes
No systemic autoimmune diseases	81/258 (31.4%)	77/244 (31.6%)	4/14 (28.6%)
Women who were or had been pregnant	144/223 (64.6%)	140/213 (65.7%)	4/10 (40.0%)
Obstetric antiphospholipid syndrome (APS) †	49/144 (34.0%)	46/140 (32.9%)	3/4 (75.0%)
No obstetric APS	95/144 (66.0%)	94/140 (67.1%)	1/4 (25.0%)
Thrombophylic risk factors			
Pregnancy/puerperium	26/155 (16.8%)‡	24/147 (16.3%)	2/8 (25.0%)
Smoking	60/258 (23.3%)	58/244 (23.8%)	2/14 (14.3%)
Hypertension (systolic >140, diastolic >90)	47/258 (18.2%)	41/244 (16.8%)	6/14 (42.9%)§
Hypercholesterolaemia (>240 mg/dl)	22/258 (8.5%)	21/244 (8.6%)	1/14 (7.1%)
BMI >85th percentile	15/258 (5.8%)	15/244 (6.1%)	0/14 (0.0%)
Pill/hormone replacement therapy	12/223 (5.4%)	12/213 (5.6%)	0/10 (0.0%)
Diabetes mellitus	5/258 (1.9%)	5/244 (2.0%)	0/14 (0.0%)
Prophylaxis			
Long-term ¶	140/258 (54.3%)	132/244 (54.1%)	8/14 (57.1%)
Only during risk situations **	68/98 (69.4%)	66/93 (71.0%)	2/5 (40.0%)

↵* 50 undifferentiated connective tissue disease, 32 autoimmune thyroiditis, 9 rheumatoid arthritis, 7 autoimmune thrombocytopenia, 7 vasculitis, 6 systemic sclerosis, 6 Sjögren's syndrome and 15 other types of autoimmune diseases (36 patients had contemporaneously more than one autoimmune diseases).

↵† 32 fetal losses (type a), 11 premature births (type b) and 13 early abortions (type c) (7 of these women had contemporaneously more than one type of pregnancy morbidity).

↵‡ Women of childbearing age.

↵§ Statistically significant ($p<0.05$).

↵¶ 138 with low-dose aspirin (LDA) and 2 with warfarin.

↵** 15 surgery/immobilisation (14 with low molecular weight heparin, 1 with warfarin), 53 pregnancy/puerperium (25 with LDA, 12 with low molecular weight heparin and 16 with both), 30 events (9 surgery/immobilisation and 21 pregnancy/puerperium) were non-treated.

Table 2

Baseline results of autoantibody assays in the antiphospholipid (aPL) carriers and their thrombosis rate.

Autoantibodies	Prevalence	Thrombotic events	
		No	Yes
IgG aCL medium/high titres	101/258 (39.1%)	95/244 (38.9%)	6/14 (42.9%)
IgM aCL medium/high titres	74/258 (28.7%)	69/244 (28.3%)	5/14 (35.7%)
IgG anti-β2GPI medium/high titres	104/258 (40.3%)	99/244 (40.6%)	5/14 (35.7%)
IgM anti-β2GPI medium/high titres	79/258 (30.6%)	74/244 (30.3%)	5/14 (35.7%)
Lupus anticoagulants	130/258 (50.4%)	119/244 (48.8%)	11/14 (78.6%)*

Autoantibodies	Prevalence	Thrombotic events	
		No	Yes
aPL antibody category I	130/258 (50.4%)	121/244 (49.6%)	9/14 (64.3%)
aPL antibody category II	128/258 (49.6%)	123/244 (50.4%)	5/14 (35.7%)
Antinuclear antibodies	163/258 (63.2%)	154/244 (63.1%)	9/14 (64.3%)
Anti-double strand DNA antibodies	33/255 (26.4%)	31/241 (12.9%)	2/14 (14.3%)
Anti-extractable nuclear antigen antibodies	52/258 (12.9%)	48/244 (19.7%)	4/14 (28.6%)

↵* Statistically significant ($p<0.05$).

aCL, anticardiolipin antibodies; anti-β2GPI, anti-β2-glycoprotein I antibodies.

Figure 1

Kaplan–Meier survival analysis and log rank test showing that the cumulative incidence of thrombotic events was significantly higher in patients with hypertension ($p<0.01$) and lupus anticoagulant ($p<0.05$).