Antiphospholipid Syndrome and Asymptomatic Carriers of Antiphospholipid Antibody: Prospective Analysis of 404 Individuals

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ABSTRACT. ***Objective.*** We carried out a prospective analysis of clinical and analytical findings in individuals with antiphospholipid antibodies (aPL).

Methods. We prospectively studied 404 individuals, classified in 2 groups: (1) patients with primary or secondary antiphospholipid syndrome (APS, n = 226); and (2) asymptomatic carriers of aPL (n = 178). Patients with APS and thrombosis were treated with dicumarin, and an international normalized ratio around 3.0 (range 2.5–3.5) was targeted. Asymptomatic carriers were not treated, but specific prophylaxis with low molecular weight heparin or aspirin was prescribed for the periods when individuals were at increased risk of thrombosis. Both groups of individuals were followed up at semester intervals for 36 months.

Results. Patients with APS presented with venous (n = 106, 46.9%) and/or arterial (n = 70. 31%) thrombosis or fetal loss (n = 58 out of 112 women of fertility age, 51.8%). At the time of the first thrombotic event, 50.0% of patients with APS had coincident risk factors for thrombosis (previous surgery and prolonged immobilization were significantly associated with venous thrombosis, and hypercholesterolemia and arterial hypertension with arterial thrombosis). Eighteen patients with APS died during the study period. Recurrence of thrombosis in patients with APS was linked to insufficient anticoagulation. During the followup, no episode of thrombosis was detected in any asymptomatic carrier. The proportion of subjects with aPL was similar in patients and in asymptomatic carriers. The proportion of subjects with aPL decreased during the followup, in both patients and carriers.

Conclusion. Differences between patients and asymptomatic carriers with aPL are at least partially dependent on the proportion of coincident vascular risk factors. The decline in aPL during the followup defines a subgroup in which an anticoagulation suppression assay could be tried. (J Rheumatol 2004;31:1560–7)

Key Indexing Terms:
ANTIPHOSPHOLIPID SYNDROME
VENOUS THROMBOSIS
ANTIPHOSPHOLIPID ANTIBODIES
ARTERIAL THROMBOSIS

The antiphospholipid syndrome (APS) is characterized clinically by the presence of venous and arterial thrombosis and recurrent fetal loss[1]. The presence of antiphospholipid antibodies (aPL) is a central serologic finding in APS and plays a critical role in diagnosis. The standard care is antithrombotic treatment after a thromboembolic event. Because the risk of recurrent thromboembolism is high, longterm anticoagulation therapy is advised in these patients[2]. However, not every patient with aPL presents recurrence of thrombosis[2-4] and the factors that influence recurrence remain controversial[5-9].

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Moreover, aPL are also present in 2% of the healthy population[10,11], and with the exception of those with high titers of antibodies, there is no clear evidence of an increased incidence of thrombosis during followup[6,10-12]. Studies analyzing the evolution of titers and presence of aPL in these individuals have not previously been performed. Similarly, the effect of planned prophylaxis in situations of increased thrombotic risk of clinical evolution in these patients is not known. We prospectively studied the clinical findings of a series of individuals distributed in 2 groups, those with APS and those without clinical signs. The evolution of aPL in both groups of individuals was analyzed.

MATERIALS AND METHODS

Patients. We prospectively studied 404 individuals, selected by the presence of aPL. They were classified into 2 groups:

(1) Patients with primary or secondary APS (n = 226). In these patients aPL concentrations were indicated according to the presence of at least one of the following characteristics: (a) patients less than 50 years old and with a first episode of thrombosis; (b) patients with 2 or more spontaneous

thrombotic events; (c) one life-threatening event (near-fatal pulmonary thromboembolism; cerebral, mesenteric, or portal venous thrombosis); (d) arterial or venous thrombosis occurring in the absence of a known predisposing factor: e.g., cancer, known thrombophilia, prolonged immobilization (i.e., lasting > 7 days) from any cause, recent trauma or surgery (i.e., within the previous 3 months), pregnancy, recent childbirth, or the use of oral contraceptives, in the case of venous thrombosis; or known cancer, thrombophilia, dyslipidemia (serum concentrations of total cholesterol > 200 mg/dl and/or triglycerides > 200 mg/dl), arterial hypertension (systolic pressure > 140 mm Hg or diastolic pressure > 90 mm Hg), obesity (body mass index > 30 kg/m^2), diabetes mellitus (baseline glycemia > 126 mg/dl), or arrhythmic, valvular or dilated cardiopathy, in the case of arterial thrombosis; or (e) recurrent fetal losses.

(2) Asymptomatic antiphospholipid antibody carriers (AAPC, n = 178). aPL concentrations were measured because of the presence of an activated partial thromboplastin time inhibitor.

With the exception of patients with APS who died during the first hospitalization, in both groups of individuals (APS and AAPC) 2 positive determinations of lupus anticoagulant (LAC) and/or anticardiolipin antibodies (aCL), assayed over an interval of 8–12 weeks, were required. A median time of 10 weeks (range 9–13 weeks) elapsed from the time thrombosis or fetal loss was diagnosed to the point the patient was recruited into the study.

Informed consent was obtained from individuals studied. The study protocol was approved by the institutional human research committee.

Patients with APS and thrombosis were treated with dicumarin, and an international normalized ratio (INR) around 3.0 (range 2.5–3.5) was targeted. Graded compression stockings were prescribed to all patients with deep-vein thrombosis of the lower extremities. Women who had had fetal loss in the absence of thrombosis were treated with aspirin (325 mg/day) if not pregnant; if they were pregnant, treatment with heparin and aspirin was indicated.

Individuals who were AAPC were not treated. However, specific prophylaxis with low molecular weight heparin (enoxaparin 1 mg/kg once daily) or with aspirin 325 mg/day was prescribed for the period when subjects were at increased risk of thrombosis: in cases of surgery or immobilization, prophylactic heparin was used; in pregnancy, low dose aspirin was indicated. Similarly, counseling and treatment to reduce vascular risk factors (diabetes, tobacco smoking, arterial hypertension, obesity) were prescribed in patients with APS and in AAPC.

Both groups were followed up at semester intervals for 36 months. At each medical visit, samples of blood were taken and a specific questionnaire was used in interviews with each patient. Particular attention was paid to occurrence of thrombotic events and additional risk factors for venous or arterial thrombosis (surgery or trauma, prolonged immobilization, cancer, nephrotic syndrome, use of estrogen-containing contraceptives or hormone replacement therapy, diabetes mellitus, arterial hypertension, hypercholesterolemia). Patients with inherited alterations (hypercoagulability states) that predispose to thrombosis were excluded. The inherited hypercoagulability states considered in this study were deficiencies of protein C, protein S, and antithrombin III, and factor V Leiden and the prothrombin G20210A mutation. Patients were tested for these abnormalities following Bauer's guidelines[13].

Definitions. APS was diagnosed according to the criteria of an international consensus statement[14]. According to Branch's definition[15], fetal loss corresponds to the death of a fetus shown to be alive at or beyond 10 weeks' gestation.

Superficial thrombophlebitis and deep venous thrombosis were confirmed by contrast venography or Doppler echography, using an Accuson Model 128 with a 5 MHz linear array probe (Accuson, Mountain View, CA, USA). Diagnosis of pulmonary emboli included perfusion-ventilation mismatches at lung scanning, helicoidal computerized tomography, or pulmonary arteriography. For diagnosis of cerebrovascular accident or ischemic stroke, neurological signs with an anatomically consistent infarction on computed tomography or magnetic resonance imaging was required. Myocardial infarction was diagnosed by acute clinical presentation with typical electrocardiographic and creatine kinase MB fraction values. Peripheral or mesenteric artery thrombosis was documented by arteriography or thrombectomy or at surgery. All these explorations were performed within 24 h of presentation.

Laboratory methods. The presence of LAC was analyzed by screening tests (dilute Russell viper venom time, dilute one-stage prothrombin time, and sensitized partial thromboplastin time) and confirmed by mixture tests (failure to correct the prolonged coagulation time by mixing the patient's plasma with normal plasma) and correction by phospholipid excess (viper venom time with phospholipid excess and platelet neutralization tests), according to the guidelines of the International Society on Thrombosis and Hemostasis[16]. Results of tests were considered abnormal only if both screening and confirmatory tests were abnormal. Patients were categorized as positive for LAC if one or more of the tests was abnormal, and were categorized as negative for LAC if mixture or confirmatory test was normal.

Anticardiolipin antibodies (immunoglobulin G and immunoglobulin M isotypes) were measured in all patients with a standardized ELISA (Orgentec Diagnostika, Mainz, Germany). The results were expressed in IgG and IgM phospholipid units according to the recommendations of the 1986 workshop on standardization of the cardiolipin test[17]. A cutoff value for serum samples was 10 GPL/ml and 7 MPL/ml for IgG and IgM aCL, respectively, according to the manufacturer's recommendation. The threshold used to distinguish moderate or high levels of aCL from low levels had not been standardized. Following Levine, *et al*[18], 20 international phospholipid units was used as the threshold separating low from moderate to high levels of aCL. aCL and LAC were less than the cutoff value in each of 20 healthy controls in whom the absence of evidence of disease was confirmed.

In those cases in which a negative result of the previously positive LAC and/or aCL occurred during the followup, a second determination, assayed at an interval of 8–12 weeks, was required.

Statistical analysis. Data are presented as mean ± standard deviation or, when indicated, as absolute number and percentage. Data from 2 independent groups were compared by the Mann-Whitney U test. Significance of parameters within each group was tested by the Wilcoxon matched-pairs signed-rank test. For qualitative variables, chi-square with Yates' correction or Fisher's exact test was used. Correlations were assessed by the method of least squares. A p value < 0.05 was considered significant.

RESULTS

Two hundred twenty-six patients with primary (n = 133) or secondary (n = 93) APS and 178 AAPC were evaluated. Associated diseases in patients with secondary APS were: (1) Connective tissue disorders in 64 patients (68.8%): systemic lupus erythematosus (SLE), n = 37; primary Sjögren's syndrome, n = 9; progressive systemic sclerosis, n = 5; rheumatoid arthritis, n = 4; mixed connective tissue disease, n = 2; other, n = 9. (2) Infectious diseases in 19 patients (20.4%): human immunodeficiency virus (HIV) infection, n = 4; chronic infection by hepatitis C virus (HCV), n = 6; coinfection by HIV and HCV, n = 9. (3) Miscellaneous in 10 patients (10.8%): non-viral liver cirrhosis, n = 4; psoriasis, n = 3; vitiligo, n = 3.

Table 1 shows the main characteristics of the individuals studied. Of those 226 patients with APS, 5 had presented arterial and venous thrombosis. Fifty-five patients were included in the study because of the obstetric history only; the other 3 cases with fetal loss also had venous (n = 2) or arterial thrombosis (n = 1).

Table 1. Demographic, clinical, and analytical characteristics of patients with antiphospholipid syndrome and asymptomatic carriers of antiphospholipid antibody.

Characteristic	Overall, n = 226	Patients with APS: Primary, n = 133	Patients with APS: Secondary, n = 93	Asymptomatic aPL Carriers, n = 178
Age, yrs, mean ± SD	44.4 ± 15.1	44.6 ± 15.2	44.0 ± 15.2	44.4 ± 17.3
Male:female ratio	1.0:1	1.0:1	1.1:1	1:1.9*
Clinical findings, n (%)				
Venous thrombosis	106 (46.9)	58 (43.6)	48 (51.6)	0
Arterial thrombosis	70 (31.0)	45 (33.8)	25 (26.9)	0
Fetal loss†	58 (51.8)	36 (53.7)	22 (48.9)	0
Analytical data				
Thrombopenia (platelet count < 125 × 10^3/mm^3), n (%)	32 (14.4)	12 (9.0)	20 (21.5)**	0 (0)*
Mean platelet count/mm^3 (× 10^3)	227 ± 100	248 ± 99	196 ± 91**	245 ± 136
Anticardiolipin antibodies IgG, n (%)	152 (67.3)	90 (67.7)	62 (66.7)	132 (74.2)
Mean IgG aCL titer, GPL/ml	37.3 ± 27.5	34.2 ± 24.5	41.6 ± 29.7	42.5 ± 40.0
Moderate–high levels of IgG aCL, n (%)††	151 (99.3)	89 (98.9)	62 (100)	130 (98.5)
IgM aCL, n (%)	63 (54.3)	35 (26.3)	28 (30.1)	53 (29.8)
Mean IgM aCL titer (MPL/ml)	17.2 ± 7.3	17.2 ± 7.4	17.2 ± 7.3	19.0 ± 12.1
Moderate–high levels of IgM aCL, n (%)††	48 (76.2)	26 (74.3)	22 (78.6)	38 (71.7)
Lupus anticoagulant, n (%)	106 (46.9)	56 (42.1)	50 (53.8)	67 (37.6)***

† Percentage of fetal losses refers to women of fertile age (primary APS, n = 67; secondary APS, n = 45). †† Percentage of individuals with moderate/high levels (> 20 international phospholipid units/ml) of anticardiolipin antibodies refers to the total number of individuals with positive antibodies. * $p < 0.001$ vs primary and secondary APS. ** $p < 0.001$ vs primary APS. *** $p < 0.05$ vs APS overall and vs secondary APS.

The percentages of venous and arterial thrombosis and recurrent fetal losses were similar in patients with primary and secondary APS. Similarly, patients with collagen disease-associated or infection-associated secondary APS presented similar frequencies of arterial [18 (24.3%) vs 7 (36.8%) cases; $p = 0.384$] and venous [35 (47.3%) vs 13 (68.4%) cases; $p = 0.126$] thrombosis. Fetal losses were very infrequent (one case) in the group with infection-associated APS due to the infrequent cases of pregnancy, probably related to the medical counseling about conception prevention given to the HIV population.

Clinical findings in patients with APS. At the time of the first thrombotic event, 50.0% of patients with APS had coincident risk factors for thrombosis; similarly, coincident risk factors for thrombosis were detectable in 27.5% of individuals who were AAPC ($p < 0.001$; Table 2). Characterization of these risk factors for thrombosis showed that previous surgery (n = 19, 17.9%) or prolonged immobilization (n = 15, 14.2%) were present in a significantly higher percentage of patients with venous thrombosis (106 patients); whereas in those with arterial thrombosis (70 patients), hypercholesterolemia (n = 19, 27.4%) or arterial hypertension (n = 17, 24.2%) were detected in a significantly higher proportion.

Fifty-eight patients had had spontaneous fetal losses (51.8% of the total women of fertile age, 112 patients). We did not detect any antecedent linked to a higher risk of abortion with the exception of the existence of previous fetal losses. No differences between patients with primary or secondary APS were detected in the prevalence of coincident risk factors.

Venous thrombosis with or without pulmonary embolism was the predominant clinical finding in both primary and secondary APS. Veins of the lower extremities were the more frequently affected. Among arterial episodes, cerebrovascular arterial occlusion was the most frequent event. Anatomic sites of thrombosis are shown in Table 3.

Baseline laboratory findings. The percentage of patients with thrombocytopenia was significantly higher and the platelet count lower in patients with secondary APS in comparison to those with primary APS. No patient who was AAPC presented thrombocytopenia.

The percentages of positivity and titers of each aPL are shown in Table 1. Although the percentage of those with aCL and the corresponding titer was similar in patients with primary and secondary APS and in AAPC, the percentage of patients with LAC was higher in secondary APS patients than in those with primary APS ($p = 0.056$) or AAPC ($p = 0.038$).

The percentage of patients with aCL, both IgG and IgM isotypes, or LAC was similar in those with venous compared to arterial thrombosis or fetal loss, in both primary and secondary APS. No significant differences were detected between mean titers of aCL in these groups (Table 4).

Table 2. Associated risk factors for thrombosis in the study population.

Coincident Risk Factor	Patients with APS			Asymptomatic aPL Carriers, n = 178
	Overall, n = 226	Primary, n = 133	Secondary, n = 93	
Previous surgery or trauma, n (%)	29 (12.8)	22 (16.5)	7 (7.5)	10 (5.6)*†
Neoplasia, n (%)	9 (4.0)	5 (3.8)	4 (4.3)	9 (5.1)
Dyslipidemia. n (%)	53 (23.5)	32 (24.1)	21 (22.6)	32 (18.0)
Arterial hypertension, n (%)	59 (26.1)	39 (29.3)	20 (21.5)	35 (19.7)
Diabetes mellitus, n (%)	24 (10.6)	16 (12.0)	8 (8.6)	20 (11.2)
Obesity, n (%)	45 (19.9)	33 (24.8)	12 (12.9)	29 (16.3)
Cardiopathy, n (%)	12 (5.3)	7 (5.3)	5 (5.4)	6 (3.4)
Prolonged immobilization, n (%)	21 (9.3)	15 (11.3)	6 (6.5)	3 (1.7)**††
Estrogen-containing contraceptive or hormone therapy, n (%)	14 (6.2)	9 (6.8)	5 (5.4)	7 (3.9)
Familiar antecedent of thrombosis, n (%)	9 (4.0)	5 (3.8)	4 (4.3)	5 (2.8)
Familiar antecedents of abortions, n (%)	1 (0.9)	1 (0.7)	0 (0)	1 (0.6)
Familiar antecedents of autoimmune diseases, n (%)	2 (1.8)	1 (1.5)	1 (2.1)	2 (1.2)
At least one risk factor, n (%)	113 (50.0)	68 (51.1)	45 (48.4)	49 (27.5)**††§

Significance of comparison between patients with APS and asymptomatic carriers of aPL: * $p = 0.017$, ** $p < 0.001$ vs APS overall. Significance of comparison between patients with primary APS and asymptomatic carriers of aPL: † $p = 0.02$, †† $p < 0.001$. Significance of comparison between patients with secondary APS and asymptomatic carriers of aPL: § $p < 0.001$. Significance of comparison between patients with primary and secondary APS: $p = 0.029$.

Table 3. Location of thrombotic episodes in patients with APS.

Location of Thrombosis	APS	
	Primary, n = 133	Secondary, n = 93
Venous thrombosis, n (%)	58 (43.6)	48 (51.6)
Lower extremities, n (%)	52 (82.9)	35 (72.9)
Upper extremities, n (%)	2 (3.4)	2 (4.2)
Central nervous system, n (%)	3 (5.2)	4 (8.3)
Abdominal veins, n (%)	0 (0.0)	2 (4.2)
Venous bypass, n (%)	1 (1.7)	0 (0.0)
Pulmonary thromboembolism without identifiable origin, n (%)	4 (6.8)	5 (10.4)
Arterial thrombosis, n (%)	45 (33.8)	25 (26.9)
Lower extremities, n (%)	10 (22.2)	10 (40.0)
Central nervous system, including retina, n (%)	32 (71.1)	7 (28.0)
Coronary arteries, n (%)	0 (0.0)	4 (16.0)
Arterial bypass, n (%)	3 (6.6)	4 (16.0)

Clinical followup. Patients with clinical APS and thrombosis were treated with oral anticoagulants. Eighteen patients with clinical APS died (9 with primary and 9 with secondary APS), all in the first 3 months. Of the 9 patients with primary APS who died, death was related to APS in all cases: thrombosis of intracranial venous sinuses, 2 cases; internal carotid thrombosis, 2 cases; bilateral renal artery thrombosis, one case; mesenteric artery thrombosis, 3 cases. In these last 2 situations (renal and mesenteric thrombosis) the cause of death was a new episode of thrombosis different from the initial one. By contrast, of the 9 patients with secondary APS who died, death was related to APS in only one case (mesenteric artery thrombosis, diagnosed during the followup), the other 8 cases being related to associated or coincident diseases. Death was related primarily to the site or severity of the thrombotic event.

We analyzed the possible variables associated with mortality from APS. None of the following variables was present in a different proportion in those patients who died, compared with survivors: sex, antecedents of diabetes, hyperlipidemia, arterial hypertension, platelet count, or positive anticardiolipin IgG or IgM or LAC. Age was also similar in survivors and nonsurvivors.

The surviving patients with APS (n = 208) were followed up for 36 months. Three of these patients with primary APS experienced recurrences of deep vein thrombosis of the

Table 4. Antiphospholipid antibodies in patients with APS, grouped according to presence or absence of arterial or venous thrombosis.

	Patients with APS					
	Overall, n = 226		Primary, n = 133		Secondary, n = 93	
	Arterial Thrombosis, n = 70	Venous Thrombosis, n = 106	Arterial Thrombosis, n = 45	Venous Thrombosis, n = 58	Arterial Thrombosis, n = 25	Venous Thrombosis, n = 48
IgG anticardiolipin antibody, n (%)	48 (68.6)	71 (67.0)	28 (62.2)	39 (67.2)	20 (80.0)	32 (66.7)
Mean titer, GPL/ml	33.4 ± 19.3	34.8 ± 25.0	29.8 ± 16.8	31.1 ± 16.0	40.0 ± 22.0	39.5 ± 32.3
Moderate–high levels of aCL IgG, n (%)*	48 (100)	70 (98.6)	28 (100)	38 (97.4)	20 (100)	32 (100)
IgM anticardiolipin antibody, n (%)	18 (25.7)	30 (28.3)	12 (26.7)	15 (25.9)	6 (24.0)	15 (31.3)
Mean titer, MPL/ml	17.3 ± 7.5	15.9 ± 5.5	18.3 ± 8.6	15.9 ± 6.1	14.9 ± 3.6	15.9 ± 4.9
Moderate–high levels of aCL IgM, n (%)	13 (72.2)	25 (83.3)	9 (75.0)	12 (80.0)	4 (66.7)	13 (86.7)
Lupus anticoagulant, n (%)	30 (42.9)	56 (52.8)	21 (46.7)	29 (50.0)	9 (36.0)	27 (56.3)

* Percentage of individuals with moderate/high levels of aCL refers to total number of individuals with positive antibodies.

lower extremities in the first 3 months, all of them in the same extremity as the first event; in all these cases, the INR, analyzed when the new thrombotic event was diagnosed, was lower than 2.5 (range 1.5–2.4). Residual manifestations of the initial thrombosis were detected in 39.5% (n = 49) of primary APS cases (post-phlebitis syndrome, 21 cases, 3 of these with recurrence of thrombosis; neurological deficits secondary to cerebrovascular arterial thrombosis, 22 cases; intermittent claudication, 6 cases) and in 46.4% (n = 39) of secondary APS cases (post-phlebitis syndrome, 22 cases; neurological deficits secondary to cerebrovascular arterial thrombosis, 6 cases; intermittent claudication, 9 cases; heart failure, 2 cases).

Bleeding complications interrupted anticoagulation in 4 patients: 3 nonfatal cases (gastric or duodenal hemorrhage secondary to peptic ulcers associated with *Helicobacter pylori* infection) and one fatal case (massive hemoptysis in a patient with bronchiectasis). All these patients had INR of 3 to 3.6 at the time of bleeding episodes. In the 3 cases of nonfatal bleeding, after treatment of *H. pylori* infection, coumarin therapy was started again and no further episodes of bleeding were noted.

Twelve AAPC received enoxaparin coincidentally with prolonged immobilization (3 cases for intervertebral disk herniation, 4 for trauma related fractures) or with surgical interventions (hysterectomy for uterine myomas, 3 cases; inguinal hernia repair, 2 cases). Aspirin was prescribed for 3 AAPC women during pregnancy. No case of thrombosis or fetal loss was detected during the followup.

Followup of laboratory abnormalities. The evolution of aPL in APS is illustrated in Figure 1. As shown, the proportion of APS patients with persistence of aCL or LAC decreased during the followup. Similar progressions were observed in the AAPC: a decrease of aCL and LAC was detected in this group. At the end of the followup, only 84.6% of APS patients and 78.0% of AAPC maintained at least one aPL.

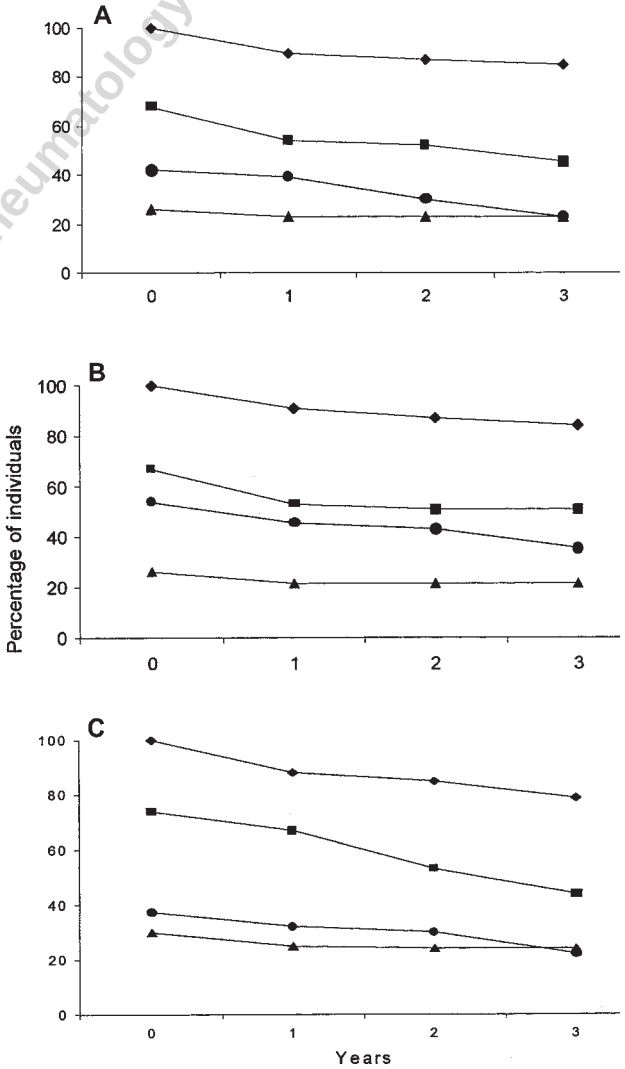

Figure 1. Percentage of patients with (A) primary and (B) secondary APS and (C) asymptomatic carriers of aPL with aCL isotypes IgG (■) and IgM (▲), LAC (●), and at least one of these antibodies (◆), during 36 month followup.

Table 5. Factors associated with the disappearance of aPL in the study population. Data are expressed as number (percentage) or as mean ± standard deviation.

Variable	APS, n = 208*		Asymptomatic Carriers of aPL, n = 178	
	Persistence of aCL, n = 176 (84.6%)	Disappearance of aCL, n = 32 (15.4%)	Persistence of aPL, n = 139 (78%)	Disappearance of aPL, n = 39 (22%)
Age, yrs	36.2 ± 7.9	42.6 ± 15.6	37.6 ± 18.8	36.7 ± 7.6
Male sex	88 (50)	15 (46.9)	47 (33.8)	14 (35.9)
Primary APS	105 (59.6)	19 (59.4)		
Clinical presentation				
Venous thrombosis	87 (49.4)	17 (53.1)		
Arterial thrombosis	47 (26.7)	11 (34.4)		
Fetal losses	30 (17.4)	6 (18.7)		
aPL at diagnosis				
IgG aCL, n (%)	109 (61.9)	19 (59.4)	104 (74.8)	28 (71.8)
IgG aCL, mean titer, GPL/ml	55.6 ± 27.8**	32.8 ± 16.3**	55.3 ± 21.3***	34.6 ± 17.7***
IgM aCL, n (%)	53 (30.1)	11 (34.3)	41 (29.5)	12 (30.8)
IgM aCL, mean titer, MPL/ml	17.3 ± 6.4	17.5 ± 7.6	18.6 ± 4.9	19.2 ± 3.4
Lupus anticoagulant, n (%)	85 (48.3)	15 (46.9)	53 (38.1)	14 (35.9)

* Patients who died (n = 18) after the diagnosis of aPL were excluded. ** p = 0.02 APS with persistence vs APS with disappearance of aCL. *** p = 0.04 asymptomatic carriers of aPL with persistence vs APS with disappearance of aCL.

Analysis of possible variables implicated in the disappearance of aPL was performed separately in APS patients and in AAPC (Table 5). Compared to the APS patients in whom aPL persisted (n = 176, 84.6%), those in whom aPL disappeared (n = 32, 15.4%) were similar in the following variables: age, sex, primary or secondary APS, clinical presentation as venous thrombosis, arterial thrombosis or fetal loss, baseline percentages of patients with positive anticardiolipin IgG or IgM isotypes or LAC. However, titers of anticardiolipin IgG antibodies were significantly higher in those in whom aPL persisted. Patients with secondary APS related to collagen diseases presented disappearance of aPL in similar proportions in the function of having or not having received immunosuppressant treatment directed against primary disease.

Similarly, in comparison with those AAPC in whom aPL persisted (n = 139), patients in whom the antibodies disappeared (n = 39) had significantly lower titers of anticardiolipin IgG antibodies at diagnosis.

DISCUSSION

We describe and compare the clinical and analytical findings from patients with APS and asymptomatic carriers of antiphospholipid antibody, in a series of 404 individuals. Two hundred twenty-six patients presented APS, with primary APS being more frequently diagnosed than secondary. As reported[18,19], not only SLE but also other collagen diseases are associated with secondary APS. Infectious diseases, mainly HIV and hepatitis C virus infections, are also associated with clinical APS. It is evident that the spectrum of autoimmune and rheumatic diseases in patients with HIV infection is increasing[20]. Thus, although HIV has previously been considered an etiology of nonpathogenic aPL, this disease was recently found to be important in clinical APS[21,22]. Similarly, HCV infection, frequently associated with some immune-mediated diseases[23], is notable as an etiologic factor in secondary APS. The subgroup of our patients with secondary APS associated with collagen diseases had clinical features similar to those associated with infectious diseases.

It is interesting that a coincident risk factor of vascular disease was detected in half of the patients with APS, a significant proportion compared with asymptomatic carriers of aPL or with the general population[24]. Moreover, risk factors were different in the cases of arterial compared with venous thrombosis. Thus, dyslipidemia and arterial hypertension were more frequently detected in those patients with arterial thrombosis; in contrast, immobilization and previous surgery were associated with venous thrombosis. The coexistence of 2 prothrombotic states increases the risk of thrombosis in a given individual[9,19] and the importance of a coincident risk factor has been stressed in several reports[5,9]. Thus, in at least half of the patients, a "second hit" could be proposed to explain the appearance of thrombosis, in accord with the multi-step etiology of thrombosis[5,9].

Arterial and venous thromboses were the most frequent clinical syndrome in APS. Thromboemboli originating from deep leg veins and thromboemboli in the cerebrovascular arteries accounted for most events, as described[3,18]. Differences in the clinical picture between primary and

secondary APS were similar to those described in other series[25,26].

By applying to patients with thrombosis a treatment in which a higher level of anticoagulation was targeted, the incidence of new thrombosis was negligible. Indeed, those cases of recurrent thrombosis were detected in patients with a level of anticoagulation less than an INR of 2.5. Evolution of the patients was characterized by persistence of residual effects of the thrombotic episodes.

A set of individuals defined as asymptomatic carriers of aPL were selected as a control group for the patients with APS. Analysis of ß$_2$-glycoprotein or other pathogenic antibodies was not performed, and there could be doubts about the pathogenetic importance of the antibodies detected in these individuals. However, these other entities were not detected in previous series[10,11,27] or in a metaanalysis of published reports[7] in which an increase of thromboembolic episodes in those with high titers of antibodies had been detected during the followup. In these studies, prophylaxis for thrombotic episodes in special circumstances, as recently proposed[28] and indicated in our patients, was not performed. Bearing in mind that prolonged or indefinite anticoagulation is indicated if thrombosis develops[29] and that recurrence of thrombosis is described preferentially in the previously-affected anatomical site[23], detection of this prothrombotic state could be an interesting measure that would allow the treatment to be limited to the period in which a coincident risk factor is present. Our series shows that in asymptomatic carriers of aPL, a zero incidence of thrombotic episodes could be predicted if these specific measures of prevention are applied.

Patients with APS and asymptomatic carriers of aPL presented aCL and LAC in a similar proportion, and the titer of aCL at diagnosis was also similar in both groups. aCL in both groups and LAC in the AAPC disappeared in 15–22% of individuals during the 36 months of followup. Whereas sex, age, clinical presentation, and percentage of each of the aPL at diagnosis were similar in those patients in whom the antibodies persisted and those in whom they disappeared, titers of IgG aCL were significantly higher in patients in whom the antibodies persisted.

One of the intriguing aspects of APS is the appropriate duration of anticoagulation. It is troubling that thrombosis frequently recurs when anticoagulation is suppressed (a recent review of retrospective and prospective studies has clearly shown a recurrence rate of 29–70% of patients[1]), particularly when aPL positivity persists[30,31]. While a prolonged duration of anticoagulation has been established, the need for indefinite treatment has not been defined. If we consider the aPL as the marker for the disease, the suppression of anticoagulation in those patients in whom the disappearance of aPL has persisted could be proposed as the alternative to indefinite continuation. This would necessarily imply testing for these antibodies during patients' followup. It is evident that a clinical trial is needed to establish if the disappearance of antibodies is definitively linked to disappearance of the risk of recurrence of thrombosis.

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