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Antiphospholipid Syndrome

Clinical and Immunologic Manifestations and Patterns of Disease Expression in a Cohort of 1,000 Patients

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Objective. **To analyze the clinical and immunologic manifestations of antiphospholipid syndrome (APS) in a large cohort of patients and to define patterns of disease expression.**

Methods. **The clinical and serologic features of APS (Sapporo preliminary criteria) in 1,000 patients from 13 European countries were analyzed using a computerized database.**

Results. **The cohort consisted of 820 female patients (82.0%) and 180 male patients (18.0%) with a mean ± SD age of 42 ± 14 years at study entry. "Primary" APS was present in 53.1% of the patients; APS was associated with systemic lupus erythematosus (SLE) in 36.2%, with lupus-like syndrome in 5.0%, and with other diseases in 5.9%. A variety of thrombotic manifestations affecting the majority of organs were recorded. A catastrophic APS occurred in 0.8% of the patients. Patients with APS associated with SLE had more episodes of arthritis and livedo reticularis, and more frequently exhibited thrombocytopenia and leukopenia. Female patients had a higher frequency of arthritis, livedo reticularis, and migraine. Male patients had a higher frequency of myocardial infarction, epilepsy, and arterial thrombosis in the lower legs and feet. In 28 patients (2.8%), disease onset occurred before age 15; these patients had more episodes of chorea and jugular vein thrombosis than the remaining patients. In 127 patients (12.7%), disease onset occurred after age 50; most of these patients were men. These patients had a**

higher frequency of stroke and angina pectoris, but a lower frequency of livedo reticularis, than the remaining patients.

Conclusion. **APS may affect any organ of the body and display a broad spectrum of manifestations. An association with SLE, the patient's sex, and the patient's age at disease onset can modify the disease expression and define specific subsets of APS.**

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by a combination of arterial and/or venous thrombosis, recurrent fetal loss, often accompanied by a mild-to-moderate thrombocytopenia, and elevated titers of antiphospholipid antibodies (aPL), namely, the lupus anticoagulant (LA) and/or anticardiolipin antibodies (aCL) (1). APS was first recognized in patients with systemic lupus erythematosus (SLE) and was then found at lower frequency in patients with other autoimmune disorders. It is now well known that the development of this syndrome may also be independent of any underlying disease (i.e., primary APS) (2). A subset of APS has recently been described in which multiple vascular occlusive events, usually affecting small vessels that supply organs and presenting over a short period of time, are the outstanding features. This subset has been called catastrophic APS (3).

Although a great variety of clinical features have been described in patients with the APS, the real prevalence of most of these manifestations is unknown (4–7). Another question that arises is whether the association with SLE, the patient's sex, or the patient's age at onset of the disease can modify the disease expression and define some specific APS subsets. Several investigators have addressed this problem, but the results have varied (8,9), probably because of the small number of patients that have been analyzed, the disparity in selection criteria for patients, and the definition of the variables.

The aim of the present study was to analyze the prevalence and characteristics of the main clinical and immunologic manifestations of APS at disease onset and during its evolution in a cohort of 1,000 APS patients. We also sought to clearly define the patterns of disease expression in this condition.

PATIENTS AND METHODS

Patient selection. The Euro-Phospholipid Project started in 1999, with a multicenter, consecutive, prospective design. In order to gather a sizeable series of patients, 20 tertiary referral centers at universities in 13 countries (Belgium, Bulgaria, Denmark, France, Germany, Greece, Hungary, Israel, Italy, The Netherlands, Portugal, Spain, and the UK) agreed to take part in the study. Staff at all 20 centers had substantial experience in the management of patients with APS.

The final cohort included 1,000 unselected patients (50 consecutive patients from each center) who met the proposed preliminary criteria for the classification of definite APS (10). Equivocal cases or cases that did not fulfill the criteria as well as cases in other previous cohort studies were not included. The patients had been attending the referral centers either as inpatients or outpatients between the years 1990 and 1999. Specifically, they attended departments of rheumatology (7 centers), clinical immunology/autoimmune diseases (6 centers), internal medicine (5 centers), and hematology/hemostasis (2 centers).

All patients had their medical histories documented and underwent a medical interview as well as a routine general physical examination by a qualified internist and/or rheumatologist. A serum sample from each patient was collected for immunologic testing. A protocol form was used to record the clinical and serologic characteristics of the patients. Salient features included in this protocol were: 1) sex, 2) race, 3) age at disease onset (defined as the initial manifestation attributable to APS), 4) age at protocol (defined as age at entry into the protocol study), 5) underlying autoimmune disease, 6) clinical manifestations at disease onset, 7) cumulative clinical manifestations during the evolution of the disease (from onset until the protocol study), and 8) laboratory features at entry into the protocol study.

Information collected into the protocol forms was transferred to a computerized database program (Access 2.0; Microsoft, Redmond, WA). The study was performed according to the principles of the Declaration of Helsinki.

Definition of clinical features. To minimize possible interobserver bias, the inclusion criteria and variables of this protocol were carefully discussed on several occasions by all the participating physicians. The underlying autoimmune disease was considered when the patient met the specific criteria, as follows: SLE, classified according to the American College of Rheumatology (ACR) revised criteria (11); lupus-like syndrome, for those who fulfilled only 2–3 ACR criteria for SLE; rheumatoid arthritis, according to the ACR criteria (12); dermatomyositis, according to the criteria of Bohan and Peter (13); systemic sclerosis, according to the ACR preliminary criteria (14); primary Sjögren's syndrome, according to the European Study Group criteria (15); systemic vasculitis, according to the ACR 1990 criteria (16); and primary APS, for those who did not fulfill classification criteria for any of the other conditions.

A total of 102 clinical manifestations that have been described in patients with APS (17) were included on the protocol forms. Patients were considered to have these manifestations if the diagnosis was confirmed according to the established criteria for each manifestation, using laboratory, imaging/Doppler, or histopathologic studies, with the exception of superficial venous thrombosis and other dermatologic features that could be diagnosed on clinical grounds. Histopathologic confirmation of thrombosis required the absence of significant evidence of inflammation in the vessel wall.

Among the major clinical manifestations, deep vein thrombosis was confirmed by Doppler studies and/or phlebography, peripheral arterial thrombosis by arteriography, cerebrovascular accident, multiinfarct dementia, cerebral venous thrombosis, and transverse myelopathy by computed tomography and/or magnetic resonance imaging scans, migraine was diagnosed if the patient fulfilled the criteria of the International Headache Society (18), pulmonary embolism was confirmed by ventilation/perfusion pulmonary scintigraphy, heart valve lesions by transthoracic echocardiogram, myocardial infarction by elevated cardiac enzyme levels and electrocardiogram, and intraabdominal infarctions by computed tomography and/or magnetic resonance imaging scans.

Patients were considered to have catastrophic APS if they presented with an acutely devastating APS with multiple organ involvement, as previously defined (3). Pregnancy morbidity was considered when the patient fulfilled the definitions established under the preliminary criteria for the classification of the APS (10).

Laboratory studies. The presence of aCL of IgG and IgM isotypes was measured by a β_2-glycoprotein I–dependent enzyme-linked immunosorbent assay (ELISA) (19). Results were considered positive if medium-to-high titers (>20 GPL or MPL units [IgG phospholipid units or IgM phospholipid units]) were present on 2 or more occasions at least 6 weeks apart. LA activity was detected by coagulation assays, adhering to the guidelines of the International Society on Thrombosis and Hemostasis (20) and according to the following steps: 1) prolonged phospholipid-dependent coagulation demonstrated on a screening test (e.g., activated partial thromboplastin time, kaolin clotting time, dilute Russell's viper venom time, dilute prothrombin time, or textarin time); 2) failure to correct the prolonged coagulation time found on the screening test by mixing the patient's sample with platelet-poor plasma from a normal donor; 3) shortening or correction of the prolonged coagulation time found on the screening test by the addition of excess phospholipid; and 4) exclusion of other coagulopathies (i.e., factor VIII inhibitor or heparin, as appropriate).

Antinuclear antibodies (ANA) were determined by indirect immunofluorescence on mouse liver and HEp-2 cell substrate. Anti–double-stranded DNA (anti-dsDNA) antibodies were determined by Farr's ammonium sulfate precipitation technique, ELISA, and indirect immunofluorescence on *Crithidia luciliae* substrate. Precipitating antibodies to extractable nuclear antigens, including Ro/SSA, La/SSB, U1 small nuclear RNP, and Sm, were detected by ELISA and counterimmunoelectrophoresis using calf and rabbit thymus and human spleen extracts. Rheumatoid factor was detected by latex and Rose-Waaler tests. All these tests were performed in referral laboratories that adhere to strict quality controls and that are participating in the standardization project of the European Forum on aPL.

Statistical analysis. Conventional chi-square and Fisher's exact tests were used for analyzing qualitative differences, and Student's *t*-test was used for comparison of means in large independent samples of similar variance. A P value less than 0.05 was considered statistically significant. When several independent variables appeared to have statistical significance in the univariate analysis, a logistic regression test was performed for multivariate analysis in order to rule out possible confounding variables. In this case, only those variables showing statistical significance in the multivariate analysis were considered to be significant study results.

Table 1. Classification of patients with antiphospholipid syndrome according to the underlying condition*

Underlying condition	No. (%) of patients
Primary antiphospholipid syndrome	531 (53.1)
Systemic lupus erythematosus	362 (36.2)
Lupus-like syndrome	50 (5.0)
Primary Sjögren's syndrome	22 (2.2)
Rheumatoid arthritis	18 (1.8)
Systemic sclerosis	7 (0.7)
Systemic vasculitis	7 (0.7)
Dermatomyositis	5 (0.5)

* There was an overlap of 2 conditions in 2 patients.

Odds ratios (ORs) were calculated to assess the risk of the presence of each variable. A lower limit of the 95% confidence interval (95% CI) that exceeded 1.0 was considered to indicate statistical significance in the case of positive association, and an upper limit that was lower than 1.0 was considered to indicate statistical significance in the case of negative association. Results of the analysis of continuous variables are reported as the mean ± SD. Statistical analyses were performed by means of the SPSS program (SPSS, Chicago, IL), using the information stored in the database program.

RESULTS

General characteristics. The cohort consisted of 820 female patients (82.0%) and 180 male patients (18.0%) (female:male ratio 5:1). There were 985 whites (98.5%), 5 blacks (0.5%), and 10 patients of other races (1.0%). The mean ± SD age at the onset of symptoms attributable to the disease was 34 ± 13 years (range 0–81 years; median 31), and the mean ± SD age at study entry was 42 ± 14 years (range 0–82 years; median 40). The mean ± SD period of evolution of the disease until entry into the study was 92 ± 75 months (range 0–200 months; median 72). Eighty-five percent of patients were diagnosed as having APS between ages 15 and 50 years.

As shown in Table 1, 53.1% of the patients had primary APS, 36.2% had APS associated with SLE, 5.0% had APS associated with lupus-like syndrome, and 5.9% associated with other diseases. A catastrophic APS occurred in 8 patients (0.8%), and in 6 of them, this was the presenting event of the APS.

Clinical manifestations. The most common presenting manifestations were deep vein thrombosis (31.7%), thrombocytopenia (21.9%), livedo reticularis (20.4%), stroke (13.1%), superficial thrombophlebitis (9.1%), pulmonary embolism (9.0%), fetal loss (8.3%),

Table 2. Clinical features at disease onset in 1,000 patients with antiphospholipid syndrome*

Manifestation	No. (%) of patients
Deep vein thrombosis	317 (31.7)
Thrombocytopenia (<100,000 platelets/μl)	219 (21.9)
Livedo reticularis	204 (20.4)
Stroke	131 (13.1)
Superficial thrombophlebitis	91 (9.1)
Pulmonary embolism	90 (9.0)
Fetal loss	83 (8.3)
Transient ischemic attack	70 (7.0)
Hemolytic anemia	66 (6.6)
Skin ulcers	39 (3.9)
Epilepsy	34 (3.4)
Pseudovasculitic skin lesions	26 (2.6)
Myocardial infarction	28 (2.8)
Amaurosis fugax	28 (2.8)
Digital gangrene	19 (1.9)

* Some patients had several associated presenting manifestations.

transient ischemic attack (7.0%), and hemolytic anemia (6.6%) (Table 2).

A great variety of clinical manifestations were recorded during the evolution of the disease in vessels of almost all organ systems. Table 3 shows the cumulative clinical features from symptom onset until entry into the study. A total of 371 patients (37.1%) presented with only venous thrombotic events, 270 (27.0%) with only arterial thrombosis, 152 (15.2%) with both venous and arterial thrombosis, 121 (12.1%) with only fetal loss, and 86 (8.6%) with only thrombosis of the microcirculation.

A total of 590 women (71.9%) experienced 1 or more pregnancies (range 1–23), and 437 of them (74.1%) succeeded in having 1 or more live births (mean 1.7; range 1–8). The most common obstetric complications in the mother were preeclampsia (9.5% of pregnant women), eclampsia (4.4%), and abruptio placentae (2.0%). The most common fetal complications were early fetal loss (35.4% of pregnancies), late fetal loss (16.9% of pregnancies), and premature birth (10.6% of live births).

Immunologic features. The main immunologic findings are summarized in Table 4. The presence of aCL was detected in 879 patients (87.9%) and LA in 536 patients (53.6%). In addition to aPL, some patients had ANA (59.7%), anti-dsDNA (29.2%), anti-Ro (14.0%), and rheumatoid factor (7.8%), among other autoantibodies. No differences were found in the clinical presentation of the APS according to the presence or absence of these antibodies.

Differences between primary APS and APS associated with SLE. Among the entire cohort, 53.1% of the patients had primary APS and 41.2% had APS associated with SLE or lupus-like syndrome. Both groups had similar profiles (including age at disease onset), except that patients with APS associated with SLE had more episodes of arthritis (56% versus 3% in patients with primary APS; $P < 0.001$, OR 37.8, 95% CI 21.9–66.1) and livedo reticularis (36% versus 16%; $P < 0.001$, OR 3, 95% CI 2.2–4.1) and more frequently exhibited thrombocytopenia (43% versus 21%; $P < 0.001$, OR 2.9, 95% CI 2.1–3.9) and leukopenia (38% versus 2%; $P < 0.001$, OR 24.5, 95% CI 13.3–46.2).

Differences related to sex. The entire cohort consisted of 820 female patients (82.0%) and 180 male patients (18.0%), with a 5:1 ratio of females to males. However, this ratio was higher in patients with SLE (7:1) than in patients with primary APS (3.5:1) ($P < 0.005$). Both female and male groups had similar clinical profiles, with the following exceptions. Female patients had more frequent episodes of arthritis (29% versus 19% in males; $P < 0.01$, OR 1.8, 95% CI 1.2–2.7), livedo reticularis (26% versus 16%; $P < 0.005$, OR 1.9, 95% CI 1.2–3), and migraine (23% versus 12%; $P < 0.005$, OR 2.2, 95% CI 1.3–3.4), while male patients more frequently had myocardial infarction (16% versus 3%; $P < 0.001$, OR 5.4, 95% CI 3–9.8), epilepsy (12% versus 6%; $P < 0.01$, OR 2.1, 95% CI 1.2–3.7), and arterial thrombosis in the lower legs and feet (11% versus 3%; $P < 0.001$, OR 3.9, 95% CI 2–7.6).

Differences related to the age at onset of APS. *Childhood-onset APS.* In 28 patients (2.8%), APS onset occurred before the age of 15 years. These patients with childhood-onset APS presented with more episodes of chorea (14% versus 1%; $P < 0.001$, OR 17.8, 95% CI 4.3–69.8) and jugular vein thrombosis (7% versus 0.1%; $P < 0.05$, OR 10.6, 95% CI 1.4–60) than the remaining patients in the cohort.

Older-onset APS. In 127 patients (12.7%), APS onset occurred after the age of 50 years. These patients with older-onset APS were more frequently male (34% versus 16%; $P < 0.001$, OR 2.8, 95% CI 1.8–4.2) and had more strokes (30% versus 18%; $P < 0.005$, OR 1.9; 95% CI 1.2–2.9) and angina pectoris (9% versus 2%; $P < 0.001$, OR 6, 95% CI 2.6–13.9), but less frequently had livedo reticularis (13% versus 26%; $P < 0.005$, OR 0.5, 95% CI 0.3–0.8), than the remaining patients in the cohort.

DISCUSSION

In the present study, we analyzed the prevalence and characteristics of the most relevant clinical and immunologic features in the largest cohort of APS patients that has been described so far. Several differ-

Table 3. Cumulative clinical features during the evolution of disease in 1,000 patients with antiphospholipid syndrome

Manifestation	No. (%) of patients
Peripheral thrombosis	
Deep vein thrombosis	389 (38.9)
Superficial thrombophlebitis in the legs	117 (11.7)
Arterial thrombosis in the legs	43 (4.3)
Venous thrombosis in the arms	34 (3.4)
Arterial thrombosis in the arms	27 (2.7)
Subclavian vein thrombosis	18 (1.8)
Jugular vein thrombosis	9 (0.9)
Neurologic manifestations	
Migraine	202 (20.2)
Stroke	198 (19.8)
Transient ischemic attack	111 (11.1)
Epilepsy	70 (7.0)
Multiinfarct dementia	25 (2.5)
Chorea	13 (1.3)
Acute encephalopathy	11 (1.1)
Transient amnesia	7 (0.7)
Cerebral venous thrombosis	7 (0.7)
Cerebellar ataxia	7 (0.7)
Transverse myelopathy	4 (0.4)
Hemiballismus	3 (0.3)
Pulmonary manifestations	
Pulmonary embolism	141 (14.1)
Pulmonary hypertension	22 (2.2)
Pulmonary microthrombosis	15 (1.5)
Fibrosing alveolitis	12 (1.2)
Other (adult respiratory distress syndrome, pulmonary hemorrhage, pulmonary artery thrombosis)	7 (0.7)
Cardiac manifestations	
Valve thickening/dysfunction	116 (11.6)
Myocardial infarction	55 (5.5)
Angina	27 (2.7)
Myocardiopathy	29 (2.9)
Vegetations	27 (2.7)
Coronary bypass rethrombosis	11 (1.1)
Intracardiac thrombus	4 (0.4)
Intraabdominal manifestations	
Renal manifestations (glomerular thrombosis, renal infarction, renal artery thrombosis, renal vein thrombosis)	27 (2.7)
Gastrointestinal manifestations (esophageal or mesenteric ischemia)	15 (1.5)
Splenic infarction	11 (1.1)
Pancreatic infarction	5 (0.5)
Addison's syndrome	4 (0.4)
Hepatic manifestations (Budd-Chiari syndrome, small hepatic vein thrombosis)	7 (0.7)
Cutaneous manifestations	
Livedo reticularis	241 (24.1)
Leg ulcers	55 (5.5)
Pseudovasculitic lesions	39 (3.9)
Digital gangrene	33 (3.3)
Cutaneous necrosis	21 (2.1)
Splinter hemorrhages	7 (0.7)
Osteoarticular manifestations	
Arthralgia	387 (38.7)
Arthritis	271 (27.1)
Avascular necrosis of bone	24 (2.4)
Ophthalmologic manifestations	
Amaurosis fugax	54 (5.4)
Retinal artery thrombosis	15 (1.5)
Retinal vein thrombosis	9 (0.9)
Optic neuropathy	10 (1.0)
Ear, nose, and throat manifestations	
Nasal septum perforation	8 (0.8)
Hematologic manifestations	
Thrombocytopenia (<100,000 platelets/μl)	296 (29.6)
Hemolytic anemia	97 (9.7)
Obstetric manifestations (n = 590 pregnant women)	
Preeclampsia	56 (9.5)
Eclampsia	26 (4.4)
Abruptio placentae	12 (2.0)
Postpartum cardiopulmonary syndrome	3 (0.5)
Fetal manifestations (n = 1,580 pregnancies)	
Early fetal loss (<10 weeks)	560 (35.4)
Late fetal loss (≥10 weeks)	267 (16.9)
Live birth	753 (47.7)
Premature birth, no. premature/no. live births	80/753 (10.6)

ences in the expression of the disease were observed in relation to the presence or absence of SLE, the patient's sex, and the patient's age at onset of APS.

This cohort consisted of 1,000 patients that have been gathered by a European consortium, the Euro-Phospholipid Project Group. This consortium was created in 1999 as part of the network promoted by the European Forum on aPL, a study group devoted to the development of multicenter projects with large populations of APS patients. The patients of the present study were collected consecutively at 20 university centers that follow all the cases diagnosed in their referral area, including all sorts of APS manifestations, and derived by a wide variety of specialists and subspecialists (i.e., internists, rheumatologists, obstetricians, hematologists, neurologists, etc.). Only patients with definite APS, as

Table 4. Immunologic findings in 1,000 patients with antiphospholipid syndrome

Parameter	No. (%) of patients
Anticardiolipin antibodies	879 (87.9)
IgG and IgM	321 (32.1)
IgG alone	436 (43.6)
IgM alone	122 (12.2)
Lupus anticoagulant	536 (53.6)
Alone	121 (12.1)
With anticardiolipin antibodies	415 (41.5)
Antinuclear antibodies	597 (59.7)
Anti–double-stranded DNA	292 (29.2)
Anti-Ro/SSA	140 (14.0)
Anti-La/SSB	57 (5.7)
Anti-RNP	59 (5.9)
Anti-Sm	55 (5.5)
Rheumatoid factor	78 (7.8)
Cryoglobulins	36 (3.6)

recommended by the international consensus statement that was recently produced in Sapporo, Japan (10), were included in the cohort, thus avoiding equivocal cases (21) or cases with only thrombocytopenia or other clinical manifestations not listed in the set of clinical criteria of the consensus statement (22). Therefore, this cohort can be considered to be representative of what are currently accepted as APS patients.

Although APS is being recognized with increasing frequency in medical practice, the diversity of its clinical and laboratory features makes precise diagnosis a challenge for the clinician, and this has been reflected in the present study. Overall, the prevalence of the major clinical features accepted as classification criteria (10) in the present cohort is comparable to that reported in previous studies (4–7). Deep venous thrombosis (38.9%), stroke (19.8%), pulmonary embolism (14.1%), superficial thrombophlebitis in the legs (11.7%), transient ischemic attacks (11.1%), and obstetric morbidity (including both fetal and maternal complications) were very common manifestations (see Table 3). However, several other manifestations that are considered "minor" in the Sapporo criteria were also frequently found, including thrombocytopenia (29.6%), livedo reticularis (24.1%), heart valve lesions (14.3%), hemolytic anemia (9.7%), epilepsy (7.0%), leg ulcers (5.5%), myocardial infarction (5.5%), and amaurosis fugax (5.4%), among others.

Additionally, the present study allowed a more precise estimate of the prevalence of a great variety of clinical features that have occasionally been reported in some patients with the APS (17,18). There were several clinical manifestations with a prevalence of 1–5%. These included arterial thrombosis in the legs (4.3%) and arms (2.7%), subclavian (1.8%) and jugular (0.9%) vein thrombosis, angina (2.7%), multiinfarct dementia (2.5%), chorea (1.3%), pulmonary hypertension (2.2%), pulmonary microthrombosis (1.5%), renal thrombosis (2.7%), and a variety of cutaneous lesions (pseudovasculitic lesions, digital gangrene, cutaneous necrosis). Finally, this study confirms that the prevalence of some other reported manifestations, such as transverse myelopathy, Addison's syndrome, and pancreatic or hepatic manifestations, is very low (<1%). It should be emphasized that these prevalences are generally lower than those reported in earlier series. A possible reason for this fact is the systematic long-term use of anticoagulants during the last decade for secondary prophylaxis of thrombotic events (23,24).

Interestingly, one of the most common clinical manifestations of the APS and, at the same time, a special characteristic among thrombophilic disorders is fetal morbidity, including abortions, fetal deaths, intrauterine growth retardation, and premature birth. Additionally, maternal morbidity (preeclampsia, eclampsia, and abruptio placentae) is also relatively common in pregnant patients with APS. The most common fetal complications in our study—where 71.9% of the women experienced 1 or more pregnancies—were early fetal loss (35.4% of pregnancies), late fetal loss (16.9% of pregnancies), and premature birth (10.6% of live births), while the most common obstetric complications in the mother were preeclampsia (9.5% of pregnant women), eclampsia (4.4%), and abruptio placentae (2.0%). However, it should be stressed that 74% of the women of the present cohort who became pregnant succeeded in having one or more live births. This represents one of the most important advances made in the last decade, after close followup and medical awareness of APS patients, together with the widespread use of antiaggregant and anticoagulant drugs (mainly, low-dose aspirin and low molecular weight heparin) and the careful monitoring of pregnancies in women with APS (25–28).

The frequencies of the major immunologic features of APS in the present series are also comparable to the frequencies reported in other studies (4–7). In addition to aPL, ANA were detected at some time during the course of the illness in 59.7% of patients, but usually at low titers, and positive titers of anti-dsDNA antibodies were found in 29.2%, always in patients who also had SLE. The other autoantibodies (anti–extractable nuclear antigens, rheumatoid factor, and cryoglobulins) were less commonly found.

This project allows us to study the patterns of disease expression in specific APS groups. Although the APS was first recognized in patients with SLE or a lupus-like syndrome (29), primary APS was the first subset that was described (2), and the present consecutive and unselected cohort study revealed that this subset is even more frequent (53.1%) than the subset associated with SLE or lupus-like syndrome (41.2%). The question of whether the features of APS are in any way influenced by the presence or absence of SLE is important for diagnostic and therapeutic reasons (30), and previous studies with smaller numbers of patients have already shown several differences (8). In the present cohort, we observed that both groups had similar profiles, with the following exceptions. Patients with APS associated with SLE had more episodes of arthritis and livedo reticularis, and more frequently exhibited thrombocytopenia and leukopenia. It is therefore reasonable to hypothesize that factors other than aPL (i.e., anti-

platelet or lymphocytotoxic antibodies) could play a role in the pathogenesis of these manifestations in SLE patients.

The majority of systemic autoimmune diseases are much more frequent in females, with a male to female ratio of 9–10:1 in SLE (31), and they appear during the childbearing years in women, mainly between ages 15 and 50 years, thus reflecting a hormonal influence in their pathogenesis. We confirmed a female predominance in this cohort (female:male ratio 5:1), but predominance was greater in patients with SLE (7:1) than in patients with primary APS (3.5:1). We observed that female and male groups in the present cohort had similar profiles, with the following exceptions. Female patients had more frequent episodes of arthritis and livedo reticularis—both connected with the higher prevalence of SLE-related APS in women—and migraine, while male patients had more frequent episodes of myocardial infarction, epilepsy, and arterial thrombosis in the lower legs and feet.

Some differences could also be detected among patients with childhood onset and older onset of the disease. Patients with childhood-onset APS had more episodes of chorea and jugular vein thrombosis, whereas patients with older-onset APS were more frequently male and had a higher frequency of strokes and angina pectoris, but a lower frequency of livedo reticularis, compared with the remaining patients.

Thus, a hormonal influence as well as other factors related to aging could be implicated in these differences. Studies to improve the identification of other APS subsets are in progress.

In 1992, the existence of a new subset of APS was described, in which multiple vascular occlusive events, usually affecting small vessels that supply organs and presenting over a short period of time, were the outstanding features. This subset was called catastrophic APS (32). Although large-vessel occlusions were also present, their prevalence did not in any way approach that in patients with classic APS. The occlusions occurred over several days to several weeks, and more than 50% of patients usually died of the disease despite seemingly adequate therapy, including anticoagulation, steroids, etc. A comprehensive review article describing the clinical and laboratory features of 50 such patients was published in 1998 (3). In the present study, the prevalence of catastrophic APS among the entire cohort of patients with APS was ~1%.

Because of the multicenter design of this study, there are several limitations. Among others, the observed prevalence of some manifestations seems to be surprisingly low. Multiple subungual splinter hemorrhages are sometimes difficult to discern, and probably not all of the cases were detected by physicians; therefore, the 0.7% prevalence may be an underestimation of the true prevalence (33). The prevalence of heart valve abnormalities was lower than previously reported (8,34), probably because a transesophageal echocardiogram was not routinely performed. Last, the 3% observed prevalence of APS-related renal manifestations is clearly an underestimation due to the frequently overlooked feature of APS nephropathy superimposed on SLE nephritis, as well as the reluctance of physicians to perform renal biopsies in APS patients who require anticoagulation and who are frequently thrombocytopenic (35).

In conclusion, this large international study has identified the prevalence and characteristics of the main clinical and immunologic manifestations of APS at its onset and during its evolution and has demonstrated that it is possible to recognize more homogeneous subsets of clinical significance. The main question that now arises is whether these APS patients with different patterns of disease expression also have a different prognosis. Our intention is to follow up this cohort of 1,000 patients during the next 10 years in order to clearly assess the morbidity characteristics and the mortality rates of the different groups of patients that have been identified.

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REFERENCES

1. Asherson RA, Cervera R, Piette JC, Shoenfeld Y. The antiphospholipid syndrome: history, definition, classification, and differential diagnosis. In: Asherson RA, Cervera R, Piette JC, Shoenfeld Y, editors. The antiphospholipid syndrome. Boca Raton (FL): CRC Press; 1996. pp. 3–12.
2. Asherson RA, Khamashta MA, Ordi-Ros J, Derksen RHWM, Machin SJ, Barquinero J, et al. The "primary" antiphospholipid syndrome: major clinical and serological features. Medicine (Baltimore) 1989;68:366–74.
3. Asherson RA, Cervera R, Piette JC, Font J, Lie JT, Burcoglu A, et al. Catastrophic antiphospholipid syndrome: clinical and laboratory features of 50 patients. Medicine (Baltimore) 1998;77:195–207.
4. Alarcón-Segovia D, Delezé M, Oria CV, Sánchez-Guerrero J, Gómez-Pacheco L, Cabiedes J, et al. Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus: a prospective analysis of 500 consecutive patients. Medicine (Baltimore) 1989;68:353–65.
5. Cervera R, Font J, López-Soto A, Casals F, Pallarés L, Bové A, et

al. Isotype distribution of anticardiolipin antibodies in systemic lupus erythematosus: prospective analysis of a series of 100 patients. Ann Rheum Dis 1990;49:109–13.
6. Mackworth-Young C, Loizou S, Walport M. Primary antiphospholipid syndrome: features of patients with raised anticardiolipin antibodies and no other disorder. Ann Rheum Dis 1989;48:362–7.
7. Font J, López-Soto A, Cervera R, Balasch J, Pallarés L, Navarro M, et al. The 'primary' antiphospholipid syndrome: antiphospholipid antibody pattern and clinical features of a series of 23 patients. Autoimmunity 1991;9:69–75.
8. Vianna JL, Khamashta MA, Ordi-Ros J, Font J, Cervera R, López-Soto A, et al. Comparison of the primary and secondary antiphospholipid syndrome: a European multicenter study of 131 patients. Am J Med 1994;96:3–9.
9. Sammaritano LR. Pediatric and familial antiphospholipid syndromes. In: Asherson RA, Cervera R, Piette JC, Shoenfeld Y, editors. The antiphospholipid syndrome. Boca Raton (FL): CRC Press; 1996. pp. 259–66.
10. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette J-C, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42: 1309–11.
11. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
12. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
13. Bohan A, Peter JB. Polymyositis and dermatomyositis. N Engl J Med 1975;292:344–7.
14. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.
15. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, et al, the European Study Group on Diagnostic Criteria for Sjögren's Syndrome. Preliminary criteria for the classification of Sjögren's syndrome: results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993;36:340–7.
16. Hunder GG, Arend WP, Bloch DA, Calabrese LH, Fauci AS, Fries JF, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Arthritis Rheum 1990; 33:1065–1144.
17. Asherson RA, Cervera R, Piette JC, Shoenfeld Y, editors. The antiphospholipid syndrome. Boca Raton (FL): CRC Press; 1996.
18. Ad Hoc Committee on Classification of Headaches. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8 suppl 7:1–96.
19. Harris EN, Gharavi AE, Patel SP, Hughes GRV. Evaluation of the anti-cardiolipin antibody test: report of an international workshop held 4 April 1986. Clin Exp Immunol 1987;68:215–22.
20. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. Thromb Haemost 1995;74:1185–90.
21. Harris EN, Pierangeli SS. "Equivocal" antiphospholipid syndrome. J Autoimmun 2000;15:81–5.
22. Lockshin MD, Sammaritano LR, Schwartzman S. Validation of the Sapporo criteria for antiphospholipid syndrome. Arthritis Rheum 2000;43:440–3.
23. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GRV. The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995;332:993–7.
24. Muñoz-Rodríguez FJ, Font J, Cervera R, Reverter JC, Tàssies D, Espinosa G, et al. Clinical study and follow-up of 100 patients with the antiphospholipid syndrome. Semin Arthritis Rheum 1999;29: 182–90.
25. Balasch J, Carmona F, López-Soto A, Font J, Creus M, Fàbregues F, et al. Low-dose aspirin for prevention of pregnancy losses in women with primary antiphospholipid syndrome. Hum Reprod 1993;8:2234–9.
26. Branch DW, Silver RM, Blackwell JL, Reading JC, Scott JR. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. Obstet Gynecol 1992;80:614–20.
27. Derksen RHWM, de Groot PG, Nieuwenhuis HK, Christiaens GCML. How to treat women with antiphospholipid antibodies in pregnancy? Ann Rheum Dis 2001;60:1–3.
28. Rai R, Cohen H, Dave M, Regan L. Randomized controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). Br Med J 1997;314:253–7.
29. Harris EN, Chan JKH, Asherson RA, Aber VR, Gharavi AE, Hughes GRV. Thrombosis, recurrent fetal loss, and thrombocytopenia: predictive value of the anticardiolipin antibody test. Arch Intern Med 1986;146:2153–6.
30. Asherson RA, Piette JC, Cervera R. "Primary," "secondary," "catastrophic," and other variants of the antiphospholipid syndrome. In: Asherson RA, Cervera R, Piette JC, Shoenfeld Y, editors. The antiphospholipid syndrome. Boca Raton (FL): CRC Press; 1996. pp. 249–58.
31. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Systemic lupus erythematosus: clinical and immunological patterns of disease expression in a cohort of 1000 patients. Medicine (Baltimore) 1993;72:113–24.
32. Asherson RA. The catastrophic antiphospholipid syndrome. J Rheumatol 1992;19:508–12.
33. Francès C, Piette JC, Saada V, Papo T, Wechsler B, Chosidow O, et al. Multiple subungual splinter hemorrhages in the antiphospholipid syndrome: a report of five cases and review of the literature. Lupus 1994;3:123–8.
34. Cervera R, Khamashta MA, Font J, Reyes PA, Vianna JL, López-Soto A, et al. High prevalence of significant heart valve lesions in patients with the "primary" antiphospholipid syndrome. Lupus 1991;1:43–7.
35. Nochy D, Daugas E, Huong DL, Piette JC, Hill G. Kidney involvement in the antiphospholipid syndrome. J Autoimmun 2000;15:127–32.

APPENDIX A: THE EURO-PHOSPHOLIPID PROJECT GROUP

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