Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicentre prospective study of 1000 patients

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ABSTRACT

Objectives: To identify the main causes of morbidity and mortality in patients with antiphospholipid syndrome (APS) during a 5-year period and to determine clinical and immunological parameters with prognostic significance.

Methods: The clinical and immunological features of a cohort of 1000 patients with APS from 13 European countries who had been followed up from 1999 to 2004 were analysed.

Results: 200 (20%) patients developed APS-related manifestations during the 5-year study period. Recurrent thrombotic events appeared in 166 (16.6%) patients and the most common were strokes (2.4% of the total cohort), transient ischaemic attacks (2.3%), deep vein thromboses (2.1%) and pulmonary embolism (2.1%). When the thrombotic events occurred, 90 patients were receiving oral anticoagulants and 49 were using aspirin. 31/420 (7.4%) patients receiving oral anticoagulants presented with haemorrhage. 3/121 (2.5%) women with only obstetric APS manifestations at the start of the study developed a new thrombotic event. A total of 77 women (9.4% of the female patients) had one or more pregnancies and 63 (81.8% of pregnant patients) had one or more live births. The most common fetal complications were early pregnancy loss (17.1% of pregnancies) and premature birth (35% of live births). 53 (5.3% of the total cohort) patients died. The most common causes of death were bacterial infection (21% of deaths), myocardial infarction (19%) and stroke (13%). No clinical or immunological predictor of thrombotic events, pregnancy morbidity or mortality was detected.

Conclusion: Patients with APS still develop significant morbidity and mortality despite current treatment (oral anticoagulants or antiaggregants, or both).

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterised by a combination of arterial and/or venous thrombosis, pregnancy morbidity and raised titres of antiphospholipid antibodies (aPL).1 To describe the course of the disease in patients with APS, we started in 1999 a multicentre observational study of 1000 European patients with a mean age of 42 years. The clinical and immunological characteristics of these patients when entered in the study have been previously reported.2 Since then, this cohort of patients has been followed up by the same doctors during the ensuing 5 years.

The aims of this study were to identify the main causes of morbidity and mortality during this period (1999–2004) and to determine clinical and immunological parameters with prognostic significance in a cohort of patients with APS.

PATIENTS AND METHODS

Patient selection

The study (“Euro-Phospholipid” project) started in 1999 with a multicentre and consecutive design. To gather a sizeable series of patients, 20 tertiary referral university centres, with substantial experience in the management of patients with APS, from 13 countries (Belgium, Bulgaria, Denmark, France, Germany, Greece, Hungary, Israel, Italy, the Netherlands, Portugal, Spain and United Kingdom) agreed to take part in the study. The final cohort included 1000 unselected patients who met the proposed preliminary criteria for the classification of definite APS.3

All patients have been followed up by the same doctors during the ensuing 5 years (1999–2004) with regular visits to the outpatient clinics at least every 3–6 months, depending on the severity of the disease and admitted to hospital if necessary. One hundred and fifty-one (15.1%) patients were lost to follow-up. The observation period stopped in 2004 or at the time of the latest patient information if lost to follow-up or at death. The study was performed according to the principles of the Declaration of Helsinki.

Definition of clinical features

To minimise possible interobserver bias and to monitor the accuracy of the data collection, a standard protocol was used and the variables of this protocol were carefully discussed by all the participating doctors on several occasions. These variables included causes of morbidity (APS manifestations and other associated medical problems), causes of death and survival. The main APS clinical manifestations evaluated in this prospective study have been previously described.7 Patients were
considered to have these manifestations if the diagnosis was firmly confirmed according to the established criteria for each manifestation using laboratory, imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis and other dermatological features that could be diagnosed on clinical grounds. For histopathological confirmation of thrombosis, no significant evidence of inflammation should be present in the vessel wall. Briefly, among the major clinical manifestations, deep vein thrombosis was confirmed by Doppler studies and/or phlebography, peripheral arterial thrombosis by arteriography, cerebrovascular accident, multi-infarct dementia, cerebral venous thrombosis and transverse myelopathy by computed tomography (CT) and/or magnetic resonance imaging (MRI) scans, pulmonary embolism was confirmed by ventilation/perfusion pulmonary scintigraphy, myocardial infarction by raised cardiac enzymes and electrocardiogram and intra-abdominal infarctions by CT and/or MRI scans. Other APS-related manifestations, but not considered as classification criteria in the international consensus statement on an update of the classification criteria for definitive APS, were thrombocytopenia (<100 × 10^9/l, confirmed at least twice 12 weeks apart), livedo reticularis, epilepsy, skin ulcers and heart valve lesions (all diagnosed according to the definitions of this consensus statement). Patients were considered to have catastrophic APS if they presented with an acutely devastating APS with multiple (>3) organ involvement, mainly affecting small vessels supplying organs and presenting over a short period of time (<1 week), as previously defined.

Pregnancy morbidity was considered when the following established definitions were fulfilled: (a) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or (b) one or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia defined according to standard definitions, or recognised features of placental insufficiency, or (c) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomical or hormonal abnormalities and maternal and maternal chromosomal causes excluded.

The main clinical manifestations related to systemic lupus erythematosus (SLE) evaluated in this study were defined according to the American Rheumatism Association glossary committee and are described in detail elsewhere. Other vascular risk factors evaluated in this study included diabetes mellitus (any previous diagnosis of diabetes or two glycaemic controls of ≥126 mg/dl), hypertension (blood pressure ≥140/90 mm Hg), hypercholesterolaemia (total cholesterol blood levels ≥200 mg/dl, high-density lipoprotein cholesterol ≤35 mg/dl and or low-density lipoprotein cholesterol ≥160 mg/dl) and smoking (>10 cigarettes/day). Diagnoses of the other associated medical problems that appeared during the study (infections, malignancies, haemorrhages, drug side effects, etc) were performed on clinical grounds and confirmed by appropriate complementary techniques. The causes of death were based on information obtained from the clinicians in charge, autopsy reports and/or death certificates.

**Laboratory studies**

The anticardiolipin antibodies (aCL) of the IgG and IgM isotypes were measured by a β2 glycoprotein I (β2GPI)-dependent enzyme-linked immunosorbent assay (ELISA). They were considered positive if present in medium to high titre (>40 GPL or >40 MPL) on two or more occasions, at least 6 weeks apart. Lupus anticoagulant (LA) activity was detected by coagulation assays according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies).

**Statistical analysis**

The following independent variables were included in the statistical analysis for the detection of possible predictors of the outcomes of interest (ie, thrombotic events, pregnancy morbidity and mortality): primary APS, SLE, gender, age at onset of APS, comorbidities (diabetes mellitus, hypertension, hypercholesterolaemia and smoking) and aPL (IgG aCL, IgM aCL and LA). Univariate and multivariate Cox proportional hazard regression tests were used to determine associations of our outcomes of interest (dependent variables) with the different independent variables. When several independent variables appeared to have statistical significance in the univariate analysis, they were included in the multivariate analysis. Results of the analysis of continuous variables are indicated as mean (SD). Survival time was defined as the interval from the time the patient entered in the study until death or last contact. Survival probabilities were calculated according to Kaplan–Meier lifetime analysis method. Statistical significance was defined as a p value <0.05.

**RESULTS**

**General characteristics at the beginning of the prospective study**

The entire cohort consisted of 220 (82.0%) female and 180 (18.0%) male patients. There were 985 (98.5%) whites, 5 (0.5%) blacks and 10 (1.0%) patients of other races. Mean (SD) age at study entry was 42 (14) years (range 0–82; median, 40). A total of 53.1% had primary APS, 36.2% had APS associated with SLE, 5.0% associated with lupus-like syndrome and 5.7% associated with other diseases. Six patients diagnosed at entry as having a primary APS developed anti-dsDNA antibodies during the 5-year study period and were reclassified as lupus-like syndrome. The main clinical manifestations at the onset of the disease, the cumulative clinical manifestations from the onset until the beginning of the study and the immunological findings when the patients entered in the study have been reported in detail elsewhere.

**APS manifestations and treatment during the study period**

Two hundred (20%) patients developed APS-related manifestations during the 5-year study period. Recurrent thrombotic events appeared in 166 (16.6%) patients and the most common were strokes (2.4% of the total cohort), transient ischaemic attacks (2.3%), deep vein thromboses (2.1%) and pulmonary embolism (2.1%). Three out of 121 (2.5%) women with only obstetric APS manifestations at the beginning of the study developed a new thrombotic event during the 5-year study period (one deep vein thrombosis, one stroke and one catastrophic APS, respectively) and only one of these patients was receiving primary thromboprophylaxis with aspirin before the thrombotic event. Nine (0.9%) patients developed an episode of catastrophic APS. Other APS-related manifestations (but not considered as classification criteria) that appeared during the study period were thrombocytopenia (5.7%), livedo reticularis (2.7%), epilepsy (1.7%), skin ulcers (1.7%) and valve thickening/dysfunction (1.7%) (table 1). After performing the multivariate analysis, no statistical differences were detected in
the occurrence of APS manifestations depending on the underlying autoimmune disease (primary APS or SLE), the gender, the age at onset of APS or the presence of comorbidities (diabetes mellitus, hypertension, hypercholesterolaemia and smoking). Neither individual aPL (IgG aCL, IgM aCL or LA) nor the combination of some of them was associated with an increased incidence of any specific clinical manifestation.

Oral anticoagulants were used in 420 (42%) patients and low-dose aspirin in 350 (35%). When the recurrent APS-related thrombotic events appeared, 90 patients were receiving oral anticoagulants (69 at a target international normalised ratio (INR) of 2–3 and 21 at a target INR >3). 49 were taking aspirin and 27 were neither anticoagulated nor antiaggregated. Thirty-one patients of 420 receiving oral anticoagulants (7.4%) developed haemorrhages (cutaneous in 18 patients, cerebral in 7, gastrointestinal in 4 and intra-abdominal in 2).

**Table 1** Main clinical manifestations related to the antiphospholipid syndrome (APS) that appeared during the 5-year follow-up (1999–2004) of the total cohort of 1000 patients

| APS manifestations* | No (% of the total cohort) |
|---------------------|--------------------------|
| Thrombocytopenia     | 37 (3.7)                 |
| Livedo reticularis   | 26 (2.6)                 |
| Stroke              | 24 (2.4)                 |
| Transient ischaemic attacks | 23 (2.3)            |
| Deep vein thrombosis | 21 (2.1)                 |
| Pulmonary embolism   | 21 (2.1)                 |
| Epilepsy            | 17 (1.7)                 |
| Skin ulcers         | 17 (1.7)                 |
| Valve thickening/dysfunction | 17 (1.7)         |
| Vegetations         | 14 (1.4)                 |
| Myocardial infarction| 9 (0.9)                  |
| Inferior extremity superficial thrombophlebitis | 9 (0.9) |
| Autoimmune haemolytic anaemia | 9 (0.9) |
| Pre-eclampsia/eclampsia | 8 (0.8)          |
| Early pregnancy loss | 18 (1.8)                 |
| Late pregnancy loss  | 7 (0.7)                  |
| Live birth with prematurity | 28 (2.8)            |
| Live birth with intrauterine growth restriction | 11 (1.1) |

*Several patients developed more than one APS-related manifestation.

**Table 2** Causes of death during the 5-year follow-up (1999–2004) of the total cohort of 1000 patients

| Causes of death* | Total No (% of deaths)† |
|------------------|-------------------------|
| Bacterial infection | 11 (20.8)               |
| Myocardial infarction | 10 (18.9)             |
| Stroke            | 7 (13.2)                |
| Haemorrhage       | 6 (11.3)                |
| Malignancy        | 6 (11.3)                |
| Catastrophic APS  | 5 (9.4)                 |
| Pulmonary embolism | 5 (9.4)                 |
| SLE pulmonary involvement | 3 (5.7) |
| SLE renal involvement | 2 (3.8)            |
| SLE central nervous system involvement | 1 (1.9) |
| Fungal infection  | 1 (1.9)                 |

*The total number of deaths was 53.
†Several patients had more than one cause of death.
APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

**DISCUSSION**

In this study we have described the main APS clinical manifestations as well as the mortality rate and the causes of death in a large cohort of European patients followed up during a 5-year-period (1999–2004). Furthermore, we have attempted to determine possible predictors of several outcomes of interest in the APS. As distinct from previous European epidemiological studies that included patients from one single country,21–24 this study covers a more representative European APS population, including patients from northern, western, southern, central and eastern Europe. The problem of a potential difference in the occurrence of APS manifestations depending on the underlying disease (primary APS or SLE), the gender, the age at onset of APS or the presence of comorbidities (diabetes mellitus, hypertension, hypercholesterolaemia and smoking). Neither individual aPL (IgG aCL, IgM aCL or LA) nor the combination of some of them was associated with an increased incidence of any specific clinical manifestation.

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APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

**Figure 1** Kaplan–Meier survival curve of the total cohort showing a 94% probability of remaining alive at 5 years from the time of entry into the study.

A total of 77 women (9.4% of female patients) had one or more pregnancies (range 1–4, total number of pregnancies 105) and 63/77 (81.8%) succeeded in having one or more live births (range 1–3, total number of live births 80). The most common fetal complications were early pregnancy loss (17.1% of pregnancies), late pregnancy loss (6.7% of pregnancies), premature birth (55% of live births) and intrauterine growth restriction (15.7% of live births).

**Mortality and causes of death during the study period**

During the study period, 53 (5.5%) patients died (21 in the first year, 12 in the second, 10 in the third, 5 in the fourth and 5 in the fifth). They included 38 female (72%) and 15 male (28%). Mean (SD) age at death was 55 (14) years (range 19–79).

The most common causes of death were bacterial infections (20.8% of deaths), myocardial infarction (18.9%), stroke (15.2%), haemorrhage (11.5%), malignancy (11.5%), catastrophic APS (9.4%) and pulmonary embolism (9.4%) (table 2). After performing the multivariate analysis, no statistical differences were detected in the causes of death depending on the underlying disease (primary APS or SLE) or the treatment that patients were receiving (immunosuppressive or anti-coagulant agents). A survival probability of 94% was found at 5 years from the time of entry into the study (fig 1). There were no differences in the survival probability depending on the underlying autoimmune disease (primary APS or SLE), the gender, the age at onset of APS, the clinical manifestations, the immunological parameters or the treatment that patients were receiving (immunosuppressive or anti-coagulant agents).

**DISCUSSION**

In this study we have described the main APS clinical manifestations as well as the mortality rate and the causes of death in a large cohort of European patients followed up during a 5-year-period (1999–2004). Furthermore, we have attempted to determine possible predictors of several outcomes of interest in the APS. As distinct from previous European epidemiological studies that included patients from one single country,21–24 this study covers a more representative European APS population, including patients from northern, western, southern, central and eastern Europe. The problem of a potential difference in the occurrence of APS manifestations depending on the underlying autoimmune disease (primary APS or SLE), the gender, the age at onset of APS, the clinical manifestations, the immunological parameters or the treatment that patients were receiving (immunosuppressive or anti-coagulant agents).
appearance or absence of the different outcome variables during the period of time that these patients participated in the study was also registered.

We have found a much lower incidence of thrombotic manifestations during this study, compared with the cumulative clinical manifestations before the start of the study (median previous period of evolution, 6 years). For instance, the frequency of deep vein thrombosis during this 5-year period was 2.1% while we had previously found a cumulative frequency of 38.9% when the patients entered into the study. Additionally, several APS-related manifestations not included in the classification criteria were similarly uncommon—namely, thrombocytopenia (3.7%), livedo reticularis (2.7%), epilepsy (1.7%), skin ulcers (1.7%) and valve thickening/dysfunction (1.7%). Interestingly, strokes and transient ischaemic attacks were the most common recurrent thrombotic events—as they appeared in 2.4% and 2.3% of the total cohort, respectively—while deep vein thromboses were the most common thrombotic events at the study entry. As most of these patients were receiving oral anticoagulants at a target INR between 2 and 3, this might indicate that this treatment mainly protects against venous thrombosis but is not sufficiently protective against arterial thrombosis.

Although the majority of patients in this cohort were receiving either anticoagulant or antiaggregant agents, 250 (23.0%) were not receiving any of these drugs during this study period. This may reflect the “real-world” situation, as many doctors are still reluctant to prescribe any drug for primary thromboprophylaxis to those female patients with APS who had experienced pregnancy morbidity or for long-term secondary thromboprophylaxis several years after the APS thrombotic event. However, 90 patients presented with a recurrent thrombotic event despite anticoagulation (21 of them at a target INR >3). This may reflect a selection bias (patients with more severe clinical manifestations may be more consistently given oral anticoagulants by their doctors), but we believe that this was probably because many patients with APS cannot keep within their target INR. Therefore, the INR at the time of the event would have much more value than the target INR but this is difficult to determine in most patients and these data were not consistently obtained in the study. On the other hand, 31/420 patients receiving oral anticoagulants (7.4%) presented with haemorrhages, 13 of them in internal organs (cerebral in seven, gastrointestinal in four and intra-abdominal in two) and in six of them, they were the main cause of death.

In this cohort, low-dose aspirin did not prevent thrombosis in 49/350 (14%) patients who were using it. Erkan et al have recently reported the results of a short trial comparing low-dose aspirin with placebo in asymptomatic, persistently aPL-positive subjects. They found a low overall annual incidence rate of arterial thrombosis. In conclusion, our study provides updated information on APS morbidity and mortality characteristics in this decade. Patients with APS still develop significant morbidity and mortality despite current treatment (mainly, oral anticoagulants and/or antiaggregant agents). These findings call for an increased effort in determining optimal prognostic markers and therapeutic measures to prevent these important complications in the APS.

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Extended report
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Appendix A: the Euro-Phospholipid Project Group (European Forum on Antiphospholipid Antibodies)

The members of the Euro-Phospholipid Project Group (European Forum on Antiphospholipid Antibodies) are as follows: Coordinators are Riccardo Cervera, Josep Font, Jean-Charles Piette, Marie-Claire Boffa, Munther A Khamashta and Graham R Hughes; from Hospital Clinic, Barcelona, Catalonia, Spain, Richard Cervera, Gerard Espinosa, Silvia Bucciarelli, Manuel Ramos-Casals, Albert Bove, Angel Robles and Juan Miguel Autón; from University Hospital, Málaga, Spain, Jean-Charles Piette, Camilla Francèse, Zahir Amoura and Marie-Claire Boffa; from St Thomas’ Hospital, London, UK, Munther A Khamashta, Cecilia N Pisoni, Maria Laura Bertolaccini and Graham RV Hughes; from Hospital Regional “Carlos Haya”, Málaga, Spain, Maria Teresa Camps and Enrique de Ramón; from Chaim-Sheba Medical Center, Tel-Hashomer, Israel, Yehuda Shoener and Giselle Goddard; from Copenhagen University Hospital at Rigshospitalet, Copenhagen, Denmark, Soren Jacobsen; from Medical and Health Science Centre, Debrecen, Hungary, Gabriella Lakos, Emese Kiss, Pal Solhasz and Margit M Zeher; from Spedali Civili, Brescia, Italy, Angela Tincani and Marco Taglietti; from Hippocration Hospital, Athens, Greece, Irene Kontopoulou-Griva, G Theodoridis and Eufrosyni Nomikou; from Policlinico “Le Scottie”, Siena, Italy, Mauro Galeazzi and Francesca Bellissi; from Istituto Auxologico, Milan, Italy, Pier Luigi Meroni and Cristina Luzzana; from University Medical Center, Utrecht, The Netherlands, Ronald H W M Derksen and Philip G de Groot; from Immunen-Krankenhaus GmbH, Berlin, Germany, Erika Gromnic-Hele; from Medical University, Sofia, Bulgaria, Marta Baleva; from Università di Pisa, Pisa, Italy, Stefano Bombarderi and Marta Mosca; from Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, Frédéric Houssaux and Chantal Lefebvre; from Centre Hospitalier Universitaire, Nîmes, France, Jean-Christophe Gris and Isabelle Quévau; from Hôpital Claude Huriez, Lille, France, Eric Hachulla and Monique Tomczak; from Hospital Geral San António, Porto, Portugal, Carlos Vasconcelos, Paulo Barbosa, Isabel Almeida, Fatima Farinha and Manuel Campos; from Technische Universität Dresden, Dresden, Germany, Beate Roch; from Hospital Clínico Universitario, Málaga, Spain, Antonio Fernández-Nebro, Manuel de Haro and Manuel Abarca.