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Antiphospholipid syndrome in northwest Italy (APS Piedmont Cohort): demographic features, risk factors, clinical and laboratory profile

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Abstract
We report the experience from the Antiphospholipid Antibodies (aPL) Regional Consortium in northwest Italy, meant to support clinical research and foster collaboration among health professionals regarding the diagnosis and management of antiphospholipid syndrome (APS) patients. This cohort-study (APS Piedmont Cohort) was designed to register the clinical characteristics at inception and associated immunological manifestations at diagnosis (if any) of patients who strictly fulfilled the current criteria for APS, all recruited at the Piedmont and Valle d'Aosta regions.
Clinical and laboratory data from 217 APS patients (171 with vascular events, 33 with pregnancy morbidity and 13 with both), from 16 centres within the geographical area were collected. Venous thrombosis was recorded in 45.6% of patients, arterial thrombosis in 35%, small-vessel thrombosis in 1.12% and mixed arterial and venous thrombosis in the remaining 19.4% of the cases. Pregnancy morbidity included 19 patients with unexplained fetal death beyond the 10th week of pregnancy, 17 with premature birth before the 34th week and 10 with three or more unexplained spontaneous abortions before the 10th week of gestation. This consortium represents an instrument by which to audit clinical practice, to provide counselling to local centres and to sustain future basic and clinical APS research.

Introduction
Seven years ago, in 2004, a consortium dedicated to the study of antiphospholipid syndrome (APS) began its activity in the Piedmont and Valle D'Aosta regions. The APS Piedmont Consortium is part of the Rare Diseases Network of the Italian National Health System Service. The main objective of this study is to describe the clinical characteristics at presentation and the associated immunological manifestations at diagnosis (if any) in patients who strictly fulfilled the updated classification criteria for APS.1 All patients were enrolled in the Interregional Register of Rare Diseases as part of the National Health System Service. The second aim is to compare the characteristics of our cohort to other published studies, mainly to the Euro-Phospholipid cohort.2 This consortium is worthy of interest for at least three reasons: (1) all patients were diagnosed and enrolled after a strict selection, according to well-established classification criteria, (2) all patients live in a well-defined geographical area and (3) all participating laboratories undergo periodically an external quality assessment (EQA) to ascertain their performance.

Patients and methods

APS Piedmont Consortium

The APS Piedmont Consortium is a group of physicians and biologists from different specialties, working in the Piedmont and Valle d'Aosta regions, an area of about 5 million inhabitants.The main aims of the consortium were: (1) to collect and record data at diagnosis, (2) to improve knowledge on diagnosis and management in the area, (3) to share current diagnostic and therapeutic strategies, (4) to discuss controversial clinical cases and (5) to support clinical and laboratory research in the field of APS.

Patient selection

The Piedmont Cohort includes 217 consecutive patients, selected from a wider group of about 400 suspected APS patients. All the enrolled patients strictly met the current classification criteria for APS.1 All cases diagnosed before 2006 were revised for Sydney criteria compliance. Patients were registered in a database program (Excel) for a scheduled follow-up visit in a tertiary hospital or university department. Data included in the database comprised: (1) gender, (2) race, (3) age at diagnosis, (4) underlying autoimmune disease, if any, (5) clinical manifestations at onset (defined as index event) and (6) laboratory profile. Conventional cardiovascular risk factors (including smoking, hypertension, hypercholesterolaemia, diabetes and family history of thrombosis), ongoing therapy before and after disease onset/relapse, and screening for inherited thrombophilia (when performed) were also registered.The study was performed according to the principles of the Declaration of Helsinki, and written consent was sought at the time of inclusion in the Interregional Register of Rare Disease — National Health System Service.

Laboratory studies

IgG and IgM anticardiolipin antibodies (aCL) and anti- β 2 glycoprotein-I (anti-β2GPI) were measured using different commercially available ELISA kits according to the proposal of the Standardization Group of the European Forum on Antiphospholipid Antibodies (aPL).3 The results of the aCL testing were expressed in GPL (1 unit IgG phospholipid) or MPL (1 unit IgM phospholipid) and those of anti-β2GPI in arbitrary units (U/ml), in accordance with the Sydney updated classification criteria.1 The cut-off values for medium/high titres for aCL were 40 GPL or MPL. Cut-off values for anti-β2GPI were calculated by the 99th percentile of healthy subjects. Lupus anticoagulant (LA) was tested according to the revised International Society on Thrombosis and Haemostasis (ISTH) three-step diagnostic strategy.4

Statistical analysis was performed by using SPSS 16.0 (Microsoft software). Two-sample t-tests, $\chi 2$ test and Fisher's exact tests were used for comparisons of continuous and categorical measures, as appropriate.

Results

General characteristics and index events from the Piedmont Cohort compared to the Euro-Phospholipid Cohort are shown in Table 1. Overall, 102 patients were diagnosed as having APS associated with other autoimmune diseases, such as systemic lupus erythematosus (SLE) (27.6%), undifferentiated connective tissue disease (UCTD) (7.3%) and other diseases (11.9%). The median age at diagnosis was 42 (range 13–80 years; mean 43.71 ± 15.31). In primary APS mean age at diagnosis was significantly higher when compared to all the cases (46.54 ± 15.9 vs. 41.13 ± 13.88, p = 0.0034). The presence of more than two conventional risk factors for thrombosis was significantly higher in patients with vascular APS compared to the ones who experienced pregnancy morbidity (odds ratio (OR) = 3.01 [95% confidence interval (CI) 1.7–6.7], p = 0.041). Low-risk inherited thrombophilic defects showed no difference in prevalence in the thrombotic vs. the obstetric subgroup. For 46 patients (21.2% of the Piedmont Cohort) the index event was a pregnancy morbidity; 99 (45.6%) had venous thromboembolism and 76 (35%) had arterial thrombosis. Laboratory results and the prevalence of the different aPL are shown in Table 2. Out of the 217 patients, 108 (49.8%) patients had more than one aPL detected (laboratory profile 1, according to Miyakis' criteria).1 Of these 108 patients, 54 exhibited a triple positivity. Furthermore, LA positivity was the most frequent aPL finding in this cohort (44.2%), an overall prevalence much higher than the 12.1% reported by the Euro-Phospholipid Cohort.2 Miyakis type 1 and 2a profiles together represented more than 93% of all APS cases; 24.9% of patients displayed triple aPL positivity. Pregnancy morbidity was the index event in 46 patients, including 19 patients with unexplained fetal deaths beyond the 10th week, 17 with premature birth before the 34th week and 10 with three or more unexplained spontaneous abortions before the 10th week.

Discussion

The Piedmont Cohort is a group of strictly selected APS patients classified according to ongoing clinical and laboratory criteria, all coming from a well-defined geographical area in northwest Italy and tested at EQA-compliant laboratories. Although a comparison with the Euro-Phospholipid Project (EURO-APS), published in 2002, was attempted, many differences attributed to the classification criteria used at the time of the diagnosis/inclusion in the cohort were found.2 In particular, in the EURO-APS cohort: (1) laboratory screening was performed using only two tests (aCL and LA), (2) tests were considered positive if aCL was above 20 GPL/MPL and were repeated after six weeks and (3) clinical manifestations such as transitory ischemic attacks (TIAs), superficial thrombophlebitis and thrombocytopaenia were also included. However, age, sex distribution at diagnosis and primary APS prevalence were similar between the cohorts, even though a female predominance was observed in previous APS series.2,6 In our cohort, we observed a higher prevalence of arterial thrombotic events (stroke plus acute myocardial infarction (AMI)) and fetal losses when compared to the EURO-APS. Concerning the aPL profile, higher risk patients are represented in the Piedmont Cohort when compared to the EURO-APS. In the Piedmont Cohort, more than 90% of patients had Miyakis type 1 or 2a aPL profile,1 among whom 25% displayed a triple positivity.7,8 In summary, the strict adherence to the ongoing recommended classification criteria allowed us to select a group of high-risk aPL and well-selected clinical profile APS patients. The aim of the Piedmont Consortium is to monitor them prospectively in an attempt to evaluate if current diagnostic and therapeutic strategies are really effective in this setting. More data from the prospective cohort will follow.

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Conflict of interest statement

None declared.

Appendix

The Antiphospholipid Piedmont Consortium includes the authors and the following members: Giachino Osvaldo, Marletto Fabio, Sosso Luisa, Marozio Luca, Data Valeria, Guida Giuseppe, Bigo Patrizia, Stella Stefania, Rollino Cristiana, Ferro Michela, Colla Loredana, Karvela Eirini, Pellerito Raffaele, Bellis Emanuela, Maina Aldo, Donvito Valentina, Nicolino Barbara, Schinco Piercarla, Sivera Piera, Kuzenko Anna, Napolitano Emanuela, Cosseddu Domenico, Marchese Cristiana (Torino). Romeo Nicoletta, Seminara Giulia (Cuneo). Stefanidou Erato Maria (Asti). Molinari Filippo (Alba). Contino Laura, Santi Roberto (Alessandria). Nallino Maria Gabriella, Calvi Roberta (Mondovì). Stratta Piero, Bizzocchi Agata, Bobbio Flavio, Sainaghi Pier Paolo, Sola Daniele (Novara).

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Table 1 General characteristics and index events in the APS Piedmont Cohort compared to the Euro-Phospholipid Cohort. 2 .

Manifestation	*Piedmont Cohort* N *(%)*	*Euro-Phospholipid Cohort* N *(%)*
Number of patients	217	1000
Classification criteria	Myakis 2006[1]	Wilson 1999[5]
Mean age at study entry	43 ± 15	42 ± 14
PAPS	115 (52.9)	531 (53.1)
Male	55 (25.3)	180 (18.0)
CAPS	3 (1.3)	8 (0.8)
Deep venous thrombosis*	81 (31.3)	317 (31.7)
Pulmonary thromboembolism	26 (12.0)	90 (9.0)
Stroke	53 (24.4)	131 (13.1)
Acute myocardial infarction	10 (4.6)	28 (2.8)
Fetal loss	38 (17.5)	83 (8.3)

APS: antiphospholipid syndrome; PAPS: primary APS; CAPS: catastrophic APS. *Some patients presented with both deep venous thrombosis and pulmonary thromboembolism.

Table 2 APL profiles in thrombotic and obstetric events, or both, at diagnosis in the APS Piedmont Cohort.

Laboratory profile[1]	*Whole cohort* N *(%)* *Tot 217*	*Thrombotic APS* N *(%)* *Tot 171*	*Obstetric APS* N *(%)* *Tot 33*	*Both obstetric and thrombotic APS* § N *(%)* *Tot 13*
Myakis 1§	108 (49.8)	85 (49.7)	17 (51.5)	6 (46.2)
Myakis 2a	96 (44.2)	78 (45.6)	12 (36.4)	6 (46.2)
Myakis 2b	11 (5.1)	6 (3.5)	4 (12.1)	1 (7.7)
Myakis 2c	2 (0.9)	2 (1.2)	–	–
Triple positivity[5]	54 (24.9)	44 (25.7)	6 (18.2)	4 (30.8)

APL: antiphospholipid antibodies; APS: antiphospholipid syndrome; § also including triple positivity; Myakis 1, more than one laboratory criteria present (any combination); Myakis 2a, lupus anticoagulant (LA) present alone; Myakis 2b, anticardiolipin (aCL) antibody present alone; Myakis 2c, anti-β_2 glycoprotein-I (anti-β_2GPI) antibody present alone. § Obstetric and thrombotic event were not concurrent at diagnosis.