Primary antiphospholipid syndrome – a retrospective study of 29 patients followed up in an autoimmune disease unit

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Abstract
The authors present a retrospective study of twenty-nine patients with primary antiphospholipid syndrome: 22 women and 7 men. The mean cohort age was 34.4 years (20-57 years). The average age, at the time of diagnosis, was 30.7 (20-53 years). The serological findings showed positive anticardiolipin antibodies in 27 patients (93%), anti-ß2-glycoprotein 1 antibodies in 25 (86%) and lupus anticoagulant in 22 patients (76%). The main manifestations included acute myocardial infarction in 2 patients, pulmonary thromboembolism in 2 patients, one patient with mesenteric thrombosis, one with venous sinus thrombosis, 10 with foetal losses (86% occurred during the second and third trimester) and 13 with deep vein thrombosis. Other clinical manifestations were thrombocytopenia in 6 patients, livedo reticularis in 4, anaemia in 3 migraine in 3, and one with transient cerebral ischemia. Four female patients had successful full-term pregnancies. Three patients had recurrent thrombosis (two with deep vein thrombosis and one pulmonary thromboembolism) despite anticoagulant treatment. The most frequent initial antiphospholipid syndrome manifestations were deep vein thrombosis (44.8%) and loss of pregnancy (34.5%). During the 29 month follow-up period (3-29 months, mean 14 months) no patients developed Systemic Lupus Erythematosus (SLE) or any other autoimmune disease.

Key words: antiphospholipid syndrome, anticardiolipin, lupus anticoagulant, autoantibodies.

Introduction
Antiphospholipid syndrome (APS), described in 1983, also known as Hughes Syndrome, is an autoimmune disease which is characterized by the occurrence of recurrent venous and/or arterial thromboses and repeated abortions (early or late), associated with the presence of antiphospholipid antibodies (APA). It was later proposed that the combination of arterial and venous events, often accompanied by thrombocytopenia, in the presence of APA, be denominated antiphospholipid syndrome, and that when it occurred in patients with systemic lupus erythematosus (SLE) or other disease of the conjunctive tissue, that it be denominated primary antiphospholipid syndrome. Analytically, it is characterized by the presence of anticardiolipin antibodies, anti-ß2-glycoprotein 1 antibodies and/or lupic anticoagulant.

The authors present a retrospective review of 29 patients with primary antiphospholipid syndrome. The main objectives of this review, besides the divulgence and sharing of experience of this pathology, were to characterize the clinical manifestations and clinical evolution presented by this group of patients.

Material and methods
The retrospective study included 40 patients with diagnosis of APL who met the diagnostic criteria for definitive APL. The patients were followed up for 3 to 29 months (average 14 months). The diagnostic criteria of APL were reviewed in 2006 and are shown in the table below (Table I).

All these patients were followed up in an External Internal Medicine/Autoimmune Diseases Clinic of the Hospital de São João, in Porto.

The data for the patients included in the study were registered in the computer database of the above-mentioned clinic. The retrospective review was based on this database and on the review of clinical processes of the patients.

The main objectives of this retrospective review were to characterize the clinical manifestations and evolution of our patients with primary APL.
To avoid the inclusion of patients with secondary APL, the exclusion criteria for the diagnosis of primary APL were used, as suggested by Piette et al. These include: malar or discoid rash, oral or pharyngeal ulcers, arthritis, pleurisy in the absence of pulmonary thromboembolism, pericarditis, persistent proteinuria > 0.5 g/24h related to glomerulonephritis, lymphopenia <1000/ml, positive anti-DNAd antibodies, positive anti-ENA antibodies and antinuclear antibodies (ANA) >1/320.

A diagnosis of SLE was considered in patients with four or more diagnostic criteria of the American College of Rheumatology.

Of these 40 patients with APL, 11 had APL secondary to SLE and 29 patients had primary APL. The clinical processes, and the records of the consultation database of patients with primary antiphospholipid syndrome, were analyzed.

Results
Of the 29 patients included in this retrospective study, and who met the current diagnostic criteria, 22 were female and 7 were male, with a ratio of 3.14:1.

The patients were followed up for a period of between 3 and 29 months (average 14 months). The average cohort age was 34.4 years (20-57 years). The average age of APL onset was APL was 30.7 years (20-53 years).

Only five patients had a family history of pathologies associated with APL, including thromboses in three patients, SLE in one patient and primary APL in another patient.

The most important thrombotic risk factors were smoking in 11 patients (37.9%), dyslipidemia in eight patients (66.7%), arterial hypertension (AHT) in three patients (10.3%), the use of oral contraceptives in two patients (6.9%) and obesity in one patient.

The main initial manifestations of APL were deep vein thrombosis in 13 patients (44.8%), repeated abortions in 10 patients (34.5%), acute myocardial infarction (AMI) in two patients (6.9%) and pulmonary thromboembolism (PTE) in two patients.

A range of thrombotic events was found, similar to those reported in the literature. In 13 patients (44.8%) episodes of deep vein thrombosis occurred (6.9%). Of these, two patients were already hypocoagulated by previous thrombotic events, and one patient already had a diagnosis of previous primary APL. In two patients (6.9%) the disease presented in the form of pulmonary thromboembolism, one of these maintained pulmonary hypertension for around 23 months after the PTE. Thrombosis of the mesenteric vein was present in one male patient (3.4%). Coronary arterial disease with AMI was present in two patients (6.9%) and was the initial episode of the disease. A pro-thrombotic study carried out subsequently demonstrated the existence of antiphospholipid antibodies, which remained positive. In one patient (3.4%) the most severe thrombotic episode was thrombosis of the venous sinuses, although this patient had already been diagnosed with primary APL.

In 10 patients (34.5%) the primary manifestation of the disease was repeated abortions, with a total of 20 cases of abortion and one stillbirth (with delayed intrauterine growth). The majority of the cases of abortion (86%) occurred in the 2nd or 3rd trimesters. During the follow-up, seven foetal losses occurred. In four patients with a history of repeated abortions, successful pregnancies were possible under therapy,

### TABLE I

**Diagnostic criteria for APL**

**Clinical criteria (1 or more must be present)**

1. 1 or more episodes of arterial, venous or small vein thrombosis affecting any tissue or organ
2. 1 or more unexplained deaths of morphologically normal foetuses at 10 or more weeks of gestation
3. 1 or more premature births of morphologically normal newborn infants at 34 or less weeks of gestation
4. 3 or more consecutive spontaneous or unexplained abortions at less than 10 weeks of gestation

**Laboratory criteria (1 or more must be present)**

1. Lupic anticoagulant present in the plasma, present on 2 or more separate occasions for at least 12 weeks
2. Anticardiolipin antibodies (IgG or IgM) at moderately high or very high levels (> 40 GPL or MPL, or > percentile 99), present on 2 or more separate occasions for at least 12 weeks, measured by the ELISA method
3. Anti-β2-glicoprotein 1 antibody (IgG or IgM) or plasma serum (at levels > percentile 99), present on 2 or more separate occasions for at least 12 weeks, measured by the ELISA method

The diagnosis can only be made if at least 1 clinical criterion and 1 laboratory criterion are present.
with newborn infants of normal weight, during the trial period.

Other clinical manifestations documented in the patients with a previous diagnosis of primary APL, were livedo reticularis in four patients (13.7%), migraine in three (10.3%) patients, and an episode of transitory ischemic accident in one patient.

The development of thrombotic events, despite the anticoagulant treatment, occurred in three patients (two PVT and one PTE), of the 19 patients receiving hypocoagulant therapy, which corresponds to 15.8%.

In relation to the analytical results obtained, other states of hypercoagulability were found in six patients (20.7%), four with Protein S deficiency and two with Protein C deficiency.

In four patients (13.7%) the existence of positive antibodies was documented, in low titres (1/100). No patient presented anti-DNA or positive anti-ENA antibodies or increase in ANA titre during the follow-up. Complement levels C3 and C4 were low in two and four patients, respectively, and in the other two patients, both fractions were decreased. Thrombocytopenia occurred in six patients (20.7%) and anemia in three (10.3%) (hemolytic anemia in one patient).

The lupic anticoagulant was positive in 22 patients (76%), anticardiolipin antibodies in 27 (93%) (18 IgG and IgM positive, seven with IgG positive and only two with IgM positive) and anti-b2-Glicoprotein 1 in 25 patients (86%) (16 with IgG and IgM positive, weight with IgM positive and only one with IgG positive).

Oral hypocoagulation was the most frequent treatment, used in 19 patients (65.5%). All the pregnant women who required hypocoagulation received low molecular weight heparins. A platelet antiagregant was used in 15 patients (51.7%) - in 10 as the sole therapy. Other medications used were antiepileptics in one patient (3.4%) (with a history of epilepsy since childhood), antidyslipidemias in eight patients (66.7%) and antihypertensors in three patients (10.3%).

No hemorrhagic complication was described in the hypocoagulated patients. There were no deaths during the follow-up period.

Discussion
In 1983, Hughes described, for the first time, patients in which clinical alterations were associated with the presence of antiphospholipid antibodies. These clinical manifestations include a tendency to arterial and venous thromboses, livedo reticularis, recurrent abortions, and occasionally, thrombocytopenia. APL is now a well-known entity. Although most early descriptions of the symptom are for patients with SLE, the concept of primary APL without association with another autoimmune disease is also recognized. The consensus in Sapporo, Japan, in 1998, provided us with simplified criteria for the classification of APL. Exclusion criteria of primary APL were proposed by Piette et al., and enable us to distinguish between these cases and those associated with SLE. In 2006, a clinical review of the diagnostic criteria for APL was carried out, and the findings are described in Table I.

Although many questions still remain, in relation to the clinical and laboratory entity, particularly diagnosis and treatment, more recent investigations and studies enable these to be addressed in a more systematized way.

Few studies have been published with long follow-up periods of patients with primary APL. The thrombotic risk factors identified are in accordance with those described in other retrospective studies published, except for the existence of diabetes mellitus, which no patient in our cohort presented. In this retrospective study, a variety of thrombotic events similar to those described in the literature was found, and it was observed that the initial manifestations of APL are in accordance with those generally found.

The prevalence of neurological manifestations was lower than that generally found in the literature, 17.2%: three patients with migraine, one patient with deep vein thrombosis and one patient with AIT. No patient presented cerebral vascular accident or other neurological manifestations of APL during the follow-up. No patient had cerebral vascular accident with initial manifestation of primary APL, as frequently occurs, according to the literature.

Abortions are a common health problem which affects 1 to 2% of healthy women of reproductive age; APL is a potentially treatable cause. The relationship between APL and repeated abortions is widely known and is frequently associated with placental infarction and thrombotic alterations in the decidual microvessels. It generally occurs after 10 weeks of gestations, unlike spontaneous abortions, which oc-
In our study, it occurred in 10 patients with initial manifestation of the disease, which is in accordance with studies already published, since it is the second most frequent initial manifestation after deep vein thrombosis.

In six patients, the coexistence of two causes of hypercoagulability was found. Associated with the presence of antiphospholipid antibodies, alterations may also occur in the remaining natural anticoagulant mechanisms, and may contribute to the thrombotic phenomena that emerge in this syndrome. One of these alterations is the decrease in free protein S (which was present in four patients). Protein S may be bound to the plasma protein C4b, or may appear in its free form, which is the active form. The proposed mechanisms for its serum reduction are an increase in affinity for C4b, which would be increased by the fact that this complement fraction is an acute phase protein, and its capacity to bind to the antiphospholipid antibodies themselves. In these four cases, this decrease may be a case of transitory deficit.

The laboratory findings are also in accordance with those described in the literature, with the exception of the presence of antinuclear antibodies, which are habitually more frequent.

It is important to emphasize that during the follow-up, no patient developed SLE or other defined autoimmune disease. This evolution appears not to be very common, according to the literature, or perhaps the evolution period is not very long. Thus, the regular monitoring of patients with primary APL is very important.

APL, whether primary or secondary, is a potentially devastating disease. The therapeutic decisions, in patients with severe thrombotic events associated with APL should be based on the literature. It is important to emphasize that there are many questions to be answered. The optimized approach in patients with arterial thromboses with persistently positive antiphospholipid antibodies, recurrent deep vein thrombosis despite anticoagulation, and evolution, evaluation and orientation of patients with suspected APL, are complicated questions that create doubts and require extensive experience that will enable prudent decisions to be made, which are appropriate for each patient.

References