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Diagnosis and classification of the antiphospholipid syndrome

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ABSTRACT

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and arterial thromboses, often multiple, and recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia, in the presence of antiphospholipid antibodies (aPL). Some estimates indicate that the incidence of the APS is around 5 new cases per 100,000 persons per year and the prevalence around 40–50 cases per 100,000 persons. The aPL are positive in approximately 13% of patients with stroke, 11% with myocardial infarction, 9.5% of patients with deep vein thrombosis and 6% of patients with pregnancy morbidity. The original classification criteria for the APS were formulated at a workshop in Sapporo, Japan, in 1998, during the 8th International Congress on aPL. The Sapporo criteria, as they are often called, were revised at another workshop in Sydney, Australia, in 2004, during the 11th International Congress on aPL. At least one clinical (vascular thrombosis or pregnancy morbidity) and one laboratory (anticardiolipin antibodies, lupus anticoagulant or anti-β_2-glycoprotein I antibodies) criterion had to be met for the classification of APS.

1. Introduction

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and arterial thromboses, often multiple, and recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia, in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or anti-β_2 glycoprotein-I (β_2GPI) antibodies [1]. The APS can be found in patients having neither clinical nor laboratory evidence of another definable condition (primary APS) or it may be associated with other diseases, mainly systemic lupus erythematosus (SLE), but occasionally with other autoimmune conditions [1], infections [2], drugs [1], and malignancies [3] (Table 1).

Primary APS patients rarely progresses to SLE. Only 8% of 128 patients, who were followed up for about 9 years, developed lupus, and a positive Coombs' test was a clinically significant predictor of progression [4].

The aPL can appear in different scenarios, such as asymptomatic "carrier" patients for aPL, "classical" APS with recurrent venous and/or arterial thrombosis, APS affecting otherwise healthy women with recurrent pregnancy loss, patients with aPL positivity with non-thrombotic aPL manifestations (i.e. thrombocytopenia, hemolytic anemia or *livedo reticularis*) [5] or, in a small subset of patients, as a life-threatening form characterized by a rapid development of microthrombosis that led to rapid multiorgan failure, which is termed catastrophic APS [6].

2. Epidemiology

Prevalence of the aPL in the general population ranges between 1 and 5%. However, only a minority of these individuals develop the APS. Some estimates indicate that the incidence of the APS is around 5 new cases per 100,000 persons per year and the prevalence around 40–50 cases per 100,000 persons [7].

Recently, the APS ACTION group (AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking) published a literature review focused in the prevalence of aPL in the general population with pregnancy morbidity, stroke, myocardial infarction (MI) and deep vein thrombosis (DVT). The authors estimated that aPL are positive in approximately 13% of patients with stoke, 11% with MI, 9.5% of patients with DVT and 6% of patients with pregnancy morbidity [8].

The prevalence of the catastrophic APS is scarce (less than 1% of all cases of APS) [6] but its potentially lethal outcome emphasizes its importance in clinical medicine today [9,10]. In order to put together all the published case reports as well as the new diagnosed cases from all over the world, an international registry of patients with catastrophic APS ("CAPS Registry") was created in 2000 by the

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European Forum on Antiphospholipid Antibodies. Currently, it documents the entire clinical, laboratory and therapeutic data of more than 400 patients whose data has been fully registered. This registry can be freely consulted at the Internet (http://infmed.fcrb.es/es/web/caps).

3. History

The association of thrombosis, recurrent fetal losses and thrombocytopenia with the LA phenomenon was observed in early publications in the 60's, but it was not until 30 years ago that Graham R.V. Hughes linked major cerebral disease (e.g. recurrent strokes) with abortions and the LA in an editorial published in the British Medical Journal [11]. The original concept of the APS, however, has been expanded over the years and now includes diverse complications as heart valve lesions, adrenal insufficiency and even avascular necrosis of bone, among many others [5,12].

A major advance came in the early 1990s with the simultaneous recognition by different groups that aPL required a plasma protein "cofactor" to bind cardiolipin on ELISA plates [13,14]. β2GP1 was identified as this cofactor. Since then, a number of "cofactors" including prothrombin, have been described.

4. Pathogenesis

Despite the strong association between aPL and thrombosis, the pathogenic role of aPL in the development of thrombosis has not been fully elucidated. Available data indicate that many of the autoantibodies associated with APS are directed against a number of plasma proteins and proteins expressed on, or bound to, the surface of vascular endothelial cells or platelets. The involvement of aPL in clinically important normal procoagulant and anticoagulant reactions and on certain cells altering the expression and secretion of various molecules may offer a basis for definitive investigations of possible mechanisms by which aPL may develop thrombotic events in patients with APS (Table 2) [15,16].

5. Clinical manifestations

The clinical picture of the APS is characterized by venous and arterial thromboses, fetal losses and thrombocytopenia. Single vessel involvement or multiple vascular occlusions may give rise to a wide variety of presentations. The baseline characteristics of a cohort of 1000 patients with APS ("Euro-Phospholipid Project") are collected in Table 3 [17]. Any combination of vascular occlusive events may occur in the same individual and the time interval between them also varies considerably from weeks to months or even years. After a 5-year follow-up of the 1000 patients with APS from the "Euro-Phospholipid Project", a bunch of new APS features appeared over time [18]. Those manifestations included thrombocytopenia (3.7%), *livedo reticularis* (2.6%), stroke (2.4%), transient ischemic attacks (2.3%), DVT (2.1%), pulmonary embolism (2.1%), epilepsy (1.7%), valve vegetations (1.4%) and MI (1%), among others.

Table 1
Diseases where aPL have been described.

Systemic autoimmune diseases: Systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, primary Sjogren's syndrome, dermato- and polymyositis, vasculitis (polyarteritis nodosa, microscopic polyarteritis, giant cell arteritis, Behçet's disease, relapsing polychondritis, leucocytoclastic vasculitis).
Infections: Viral (HIV infection, mononucleosis, rubella, parvovirus, hepatitis A, B, C, mumps), bacterial (syphilis, Lyme disease, tuberculosis, leprosy, infective endocarditis, rheumatic fever, *Klebsiella*), protozoal (malaria, toxoplasmosis).
Malignancies: Solid tumors (lung, colon, cervix, prostate, liver, kidney, thymus, esophagus, maxilla, ovary, breast), hematologic (myeloid and lymphatic leukemias, polycythemia vera, myelofibrosis), lymphoproliferative diseases (Hodgkin's disease, non-Hodgkin's lymphoma, lymphosarcoma, cutaneous T-cell lymphoma/Sezary syndrome), paraproteinemias (monoclonal gammapathies, Waldenström macroglobulinemia, myeloma).
Non-malignant hematologic conditions: Idiopathic thrombocytopenic purpura, sickle cell disease, pernicious anemia.
Drugs: Procainamide, phenothiazines, ethosuximide, chlorothiazide, quinine, oral contraceptives, anti-TNFα therapies.
Other conditions: Diabetes mellitus, autoimmune thyroid disease, inflammatory bowel diseases, dialysis, Klinefelter's syndrome, Ehlers–Danlos syndrome.

6. Laboratory abnormalities

A wide variety of laboratory abnormalities can be found in patients with APS, depending on the organ involvement. The most common immunological features are depicted in Table 4. Detection of the LA must be performed according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies) [19].

7. Classification criteria

In 1999, a preliminary classification criterion was established after an expert workshop held in Sapporo, Japan [20]. More recently, another workshop was held in Sydney, Australia, in which the experts proposed some modifications to the previous criteria, such as the inclusion of anti-β2GPI antibodies. Although no new clinical criteria were added, some particular features were remarked on, such as associated APS features, including cardiac valve involvement, *livedo reticularis*, thrombocytopenia, APS nephropathy, and non-thrombotic central nervous system manifestations (i.e. cognitive dysfunction) [21] (Table 5).

The preliminary classification criteria for catastrophic APS were formulated at a workshop in Taormina, Italy, in 2002, during the 10th International Congress on aPL, and published as a consensus statement in 2003 (Table 6) [22].

8. Assessment of the classification criteria

The revised APS classification criteria [21] provide a more uniform basis for selecting patients for APS research by emphasizing

Table 2
Possible pathogenic mechanisms of the aPL [15,16].

Inhibition of anticoagulant reactions
Inhibition of β_2GPI anticoagulant activity
Inhibition of the protein C pathway
Inhibition of protein C activation
Inhibition of activated protein C
Inhibition of antithrombin activity
Displacement of annexin A5
Cell-mediated events
On endothelial cells
Enhanced endothelial cell procoagulant activity
Increased expression and activation of tissue factor
Expression of adhesion molecules
Impaired fibrinolysis
Dysregulation of eicosanoids
Decreased endothelial cell prostacyclin production
Increased platelet thromboxane A_2 production
Impaired function of endothelial nitric oxide synthase
On monocytes
Expression of tissue factor
Increase oxidative stress
On platelets
Enhanced platelet activation/aggregation
On plasmacytoid dendritic cells
Increased expression of toll-like receptor 7 and toll-like receptor 8