Antiphospholipid Syndrome Review

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• Antiphospholipid syndrome • Lupus • Anticoagulant
• Anticardiolipin • β2 glycoprotein I

The antiphospholipid syndrome (APS) is an autoimmune disorder presenting with tissue injury in various organs attributed to large or small vessel thrombosis or, in some instances, possible nonthrombotic inflammatory mechanisms, associated with in vitro evidence of antibodies to certain proteins, or protein-phospholipid complexes. Clinicians in nearly every discipline encounter patients of all ages with presentations that lead to consideration of APS in the differential diagnosis, especially in obstetrics, rheumatology, hematology, neurology, cardiology, vascular medicine, and dermatology. Like a mirage, however, although the pathophysiology, diagnosis, and management of APS may seem clear and straightforward from a distance, closer inspection reveals a more complex, incomplete, and uncertain image. This article reviews the evolution of APS from the first description of lupus anticoagulant (LAC) to the current criteria used to guide clinical research, critiques laboratory methods used to identify autoantibodies, comments on prognosis and management, and summarizes insights into the pathophysiology of this elusive disorder.

EVOLUTION OF THE ANTIPHOSPHOLIPID SYNDROME

Three observations, over 28 years, provide examples of the gradual development of an association between circulating anticoagulants and adverse events. In 1952, Conley and Hartmann[1] coined the term ''lupus anticoagulant'' to describe prolonged whole blood clotting times in two women diagnosed with lupus erythematosus who did not manifest abnormal bleeding or bruising tendencies. Both women also had biologic false-positive tests for syphilis. In 1963, Bowie and colleagues[2] at the Mayo Clinic reported an association between circulating anticoagulants, based on incomplete correction of either a prolonged prothrombin time (PT) or recalcification time (equivalent to a partial thromboplastin time) on 50:50 mixing with normal plasma, and thrombotic complications in 11 systemic lupus erythematosus (SLE) patients. Six of the patients also had biologic false-positive tests for syphilis. In 1980, French investigators reported fetal loss and venous thrombosis associated with circulating

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inhibitors in three women who did not have SLE.[3] The phospholipid-dependent behavior of LAC and the observation that many LAC-positive SLE patients also had biologically false-positive tests for syphilis led a group of rheumatologists at the Hammersmith Hospital in London to develop a sensitive radioimmunoassay for antibodies to cardiolipin, the negatively charged phospholipid antigen in the VDRL reagent.[4] Cohort studies confirmed associations between phospholipid antibodies (anticardiolipin [aCL] and LAC), and thrombosis, pregnancy loss, or thrombocytopenia in patients without[5] and with[6] SLE, leading to the designations of primary and secondary APS, respectively.

Conversion to an ELISA method[7] to detect aCL antibodies stimulated unbridled testing of patients with various vascular and autoimmune disorders without consistent guidelines for performing or interpreting aCL results. Investigators were also reporting positive aCL antibodies associated with acute infections and adverse drug reactions, indicating that aCL antibodies were not specific for APS. Recognizing the need for specific APS classification criteria to advance understanding of the underlying pathophysiology and to improve diagnosis and management of this complex disorder through recruitment of fairly homogeneous patient populations for future studies, experts developed initial clinical criteria and laboratory testing guidelines, which have been periodically revised based on expert consensus and clinical evidence of variable strength (**Table 1**). The first classification, proposed by the Hammersmith group, and widely adopted, included three clinical categories (arterial and venous thromboembolic events, pregnancy loss, and thrombocytopenia) and two laboratory criteria (LAC and cardiolipin antibodies), the latter restricted to IgG or IgM isotypes with titers greater than 20 affinity purified IgG or affinity purified IgM units, respectively.[8] The units were based on a calibrator derived from the sera of selected positive aCL patients. Patients who exhibited at least one clinical criteria and one repeatedly positive laboratory test, to exclude patients temporarily positive because of acute infections or possible drug reactions, were classified as having APS. Subdivision into primary and secondary APS was based on the absence or presence of SLE or other connective tissue disorders, respectively.

In 1995, recognizing the need for more consistent LAC test performance, the International Society of Thrombosis and Haemostasis Subcommittee on LAC/Phospholipid-Dependent Antibodies published general guidelines consisting of four steps (**Table 2**).[9] (1) Sensitivity is to enhance by using at least two different methods to activate clotting in the presence of a limited amount of phospholipid. (2) Specificity is improved by including a mixing step to rule out coagulopathies, and (3) a confirm step to demonstrate shortening of the clotting time, was dependent on addition of phospholipid. A plasma sample that fulfills the criteria for LAC based on steps 1 to 3 may still be a false-positive result if a high titer factor VIII inhibitor were present and an intrinsic pathway activator was used, or the plasma contained certain anticoagulants. (4) The final step requires ruling out the possibility of a false-positive LAC result by performing selected coagulation factor activities, or obtaining clinical information regarding the patient's medications and signs and symptoms of bleeding.

In 1998, an international multidisciplinary symposium workshop reviewed the growing body of evidence combined with expert experience and opinion and updated the classification criteria for APS (see **Table 1**).[10] Major changes included the removal of thrombocytopenia as a clinical criterion because of insufficient evidence of an independent association with antiphospholipid antibodies, addition of specific criteria for pregnancy complications attributed to phospholipid antibodies, inclusion of the International Society of Thrombosis and Haemostasis guidelines for LAC testing, and the requirement that aCL antibody testing methods include β_2 glycoprotein I (β2GPI).