Antiphospholipid Syndrome

Feature

Disease Facts

**Synonyms**

Antiphospholipid antibody syndrome, Hughes syndrome.

**Epidemiology**

The incidence of patients with asymptomatic APS is unknown. Antiphospholipid antibodies (lupus anticoagulants and anticardiolipin antibodies) are present in 1-5% of the general population, and in about 50% of patients with systemic lupus erythematosus (SLE) and other autoimmune diseases. Approximately 40,000 new patients develop arterial or venous thrombosis per year in the United States from primary or secondary APS. The median age of new patients is approximately 30 years, with a male:female ratio of about 1:3.

**Etiology & Pathogenesis**

Since the initial description of APS more than 20 years ago, numerous associations of antiphospholipid antibodies with various infectious diseases, drugs, and autoimmune diseases lead to many conflicting theories of its etiology. Although anionic phospholipids were long believed to be the antigenic targets for antiphospholipid antibodies, it has become apparent in recent years that the actual target is β2-glycoprotein I (β2-GPI), a plasma protein with strong affinity for negatively charged macromolecules such as anionic phospholipids. Very recently, the discovery of shared peptide sequences between β2-GPI and some microorganisms, particularly Saccharomyces cerevisiae, has lead to the hypothesis that at least some cases of APS may not be of primary autoimmune origin, but due to molecular mimicry. β2-GPI has complex interactions with the coagulation system that are poorly understood at present.

**Clinical Presentation**

APS is clinically defined by the presence of one or more antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibody) and/or a biologic-false positive test for syphilis (FPTS) accompanied by the simultaneous or subsequent development of any one or more of a number of APA-affiliated clinical manifestations. These include venous thrombosis, arterial thrombosis, obstetrical complications, thrombocytopenia, bleeding, neurological disease (transient ischemic attacks (TIA’s) and stroke, early-onset dementia, amaurosis fugax and retinal venous or arterial thrombosis, etc.), skin lesions (livedo reticularis, etc.), cardiac valve vegetations and mitral regurgitation, myocardial dysfunction, primary pulmonary hypertension, and adrenal insufficiency.

Primary APAS is thrombosis and or obstetrical complications in association with antiphospholipid antibodies, but without signs of connective tissue disease, while secondary APAS refers to those patients with systemic lupus erythematosus (SLE) who also have an APA. Before a definitive diagnosis of primary APAS can be made, at least two years of careful clinical observation are necessary to rule out early SLE, and one of the tests for APA should be positive on two occasions at least three months apart. Overall, autoimmune disease is present, or subsequently identified, in approximately 20% of patients with APAs.

APAs develop in patients receiving certain drugs, and in a miscellaneous group of patients with a variety of diseases, including malignancy, HIV and other viral infections. Therapeutically administered drugs affiliated with APAs include phenytoin, chlorpro-mazine, dilantin, quinidine, procainamide, and some antibiotics.
## Antiphospholipid Syndrome

### Clinical Presentation (Cont’d)

Rare APA patients present with acute multi-organ involvement, including signs and symptoms of encephalopathy, seizures, livedo reticularis, renal insufficiency, pulmonary failure, and multiple thrombi involving both large and small vessel occlusions. The term "catastrophic APA syndrome" and "Asherson syndrome" has been applied to this disease, which is associated with high-titered APAs and a high mortality rate.

### Laboratory Features

The laboratory diagnosis of a LA is based on the initial finding of an abnormal phospholipid-dependent clotting assay, followed by confirmation that a clotting inhibitor is present, and that the inhibitor is dependent on phospholipid. Unfortunately, the heterogeneous nature of LAs limits the sensitivity and specificity of individual coagulation assays for LA detection and analysis; multiple assays are usually required and there is no standard method of approach. However, the initial laboratory evaluation will usually show a prolonged activated partial thromboplastin time (aPTT) with a normal to slightly prolonged prothrombin time (PT). An aPTT mixing study is necessary to identify the cause of the elevated aPTT and establish the presence of an inhibitor.

The Russell Viper Venom Time (RVVT) is the most widely used clinical laboratory assay for confirmation of the presence of a phospholipid-dependent antibody. Russell’s viper (Vipera russellii) is a large venomous snake native to India and Southeast Asia. Russell’s viper venom (RVV) causes massive thrombosis when injected *in vivo*. The coagulant protein of RVV is an enzyme (serine protease) which directly activates factor X in the presence of Ca++, bypassing the intrinsic and extrinsic pathways. The activated factor X then activates prothrombin in the presence of factor V and phospholipid.

The dilute Russell Viper Venom Time (dRVVT) uses a “diluted” venom concentration and minimal phospholipid concentration to give a clotting time of 23 to 27 seconds with normal serum. Under these circumstances, the clotting time becomes very sensitive to the presence of phospholipid. LAs bind the available phospholipid, block the activation of factor II, and lead to a prolongation of the clotting time. The dRVVT is more specific for LA than the aPTT since it is not influenced by deficiencies of the contact or intrinsic pathway factors or antibodies to factors VIII, IX, or XI. The dRVVT can be used to detect LA in patient samples with a normal aPTT since phospholipid dilution increases the sensitivity of the assay. A commercially available dRVVT test reagent, (DVTest, American Diagnostica, Inc., Greenwich, CT) combines RVV, plant phospholipid, and calcium into a single reagent. A second reagent, containing RVV, extra plant phospholipid, and calcium is usually available to “confirm” a positive result. The extra phospholipid in the confirm reagent corrects a prolonged dRVVT time in a manner analogous to platelet addition in the aPTT-based platelet neutralization procedure.

Other confirmatory assays for phospholipids-dependent antibodies include the hexagonal phospholipid assay, PNP, tissue thromboplastin inhibition (TTI) assay, textarintine, kaolin clotting time (KCT). Because of individual variability in laboratory results, a positive findings in at least two assays is recommended for diagnostic confirmation.

Anti-cardiolipin antibodies are detected by ELISA assays utilizing microliter plates coated with dried cardiolipin. Bovine albumin or fetal calf serum is added to block non-specific binding sites, serum specimens are incubated in the microtiter wells, followed by washing to remove serum and unbound immunoglobulin, and incubation with monospecific or polyvalent enzyme-labeled anti-human immunoglobulin. Affinity-purified, isotype specific ACAs and a series of international workshops in the 1980’s resulted in standardized methodology and the definition of standard units of anticardiolipin activity (GPL and MPL). One GPL or MPL unit is equivalent to one mg/mL of an affinity-purified standard IgG or IgM sample obtained from specified individuals. Later assays utilized negatively-charged phospholipids instead of cardiolipin.

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The treatment of APS is based on the severity of clinical manifestations, particularly thrombosis, and whether the patient has the primary or secondary form of the disease. Aspirin is the cornerstone of treatment in patients without a history of thrombosis, with hydroxychloroquine added in patients with SLE. Patients with a single episode of thrombosis are at a high risk of recurrent thrombotic disease, and require lifelong anticoagulation, currently with warfarin. Pregnant women with APS are usually treated with heparin or low molecular weight heparin to prevent pregnancy loss. Other forms of treatment may include corticosteroids or intravenous immunoglobulin.

### Treatment

- Harris EN, Khamashta M: Anticardiolipin test and the antiphospholipid (Hughes) syndrome: 20 years and counting! J Rheumatol 31:2099, 2004
References (Cont’d)

Harris EN, Pierangeli SS: Revisiting the anticardiolipin test and its standardization. Lupus 11:269, 2002


