Antiphospholipid Syndrome: An Overview

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This paper reviews antiphospholipid syndrome (APS), also known as Hughes syndrome, which is a potentially life-threatening autoimmune disorder where the body produces antibodies directed toward phospholipids and phospholipid-binding proteins. Diagnosis of this syndrome relies on both clinical and laboratory criteria. Laboratory testing used for diagnosing APS includes coagulation assays for the detection of lupus anticoagulant (LA) and enzyme-linked immunosorbent assay (ELISA) for antiphospholipid antibody (APL) detection.

ABBREVIATIONS: APL = antiphospholipid antibodies; APS = antiphospholipid syndrome; APTT = activated partial thromboplastin time; β_2-GPI = beta$_2$-glycoprotein I; dRVVT = dilute Russell's viper venom time; ELISA = enzyme-linked immunosorbent assay; Ig = immunoglobulin; KCT = kaolin clotting time; LA = lupus anticoagulant.

INDEX TERMS: antiphospholipid syndrome; antiphospholipid antibodies; laboratory techniques and procedures; lupus anticoagulant.

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APS, which was first described by Graham Hughes in 1983,[1] is an auto-immune disorder that is characterized by the presence of APL, arterial and/or venous thrombosis, and repeated pregnancy loss. The syndrome is categorized as primary or secondary based on whether it occurs alone (primary APS) or in the presence of other diseases (secondary APS), primarily autoimmune disorders such as systemic lupus erythematosus.[2] Patients with APS progress seldom to the catastrophic form of this disorder which is characterized by multiple organ infarcts transcending to multiple organ failure within days. The syndrome is more commonly noted in young to middle-aged adults and exhibits a female predominance.[3] APL can occur in connective tissue disorders, infectious disease states such as syphilis and AIDS, and may be drug induced. They can also occur incidentally in healthy individuals and as a result, APL are considered clinically significant only when present in APS.[4]

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Mechanisms of pathogenicity

In APS, APL consist of LA, anticardiolipin antibodies, and anticardiolipin antibodies that recognize specific target molecules such as beta$_2$-glycoprotein I (β_2-GPI), prothrombin, protein C, protein S, and annexin V.[5,6] The exact mechanism in which these antibodies cause or promote thrombosis is not known; however, it is clear that multiple mechanisms are involved. One study was aimed at determining the IgG subclass distribution of anticardiolipin and anti-β_2-GPI antibodies and the clinical manifestations of each subclass. This study found that different IgG subclasses (anti-β_2-GPI IgG$_2$, anti-β_2-GPI IgG$_3$, anticardiolipin IgG$_2$), which differ in their effector functions, were associated with the same syndrome manifestations (arterial and/or venous thrombosis and fetal loss).[7] A second study investigating the genetics of β_2-GPI, a naturally occurring anticoagulant, found that β_2-GPI concentration varied in healthy populations and even identified β_2-GPI congenitally deficient siblings. Interestingly, the siblings did not exhibit a history of thrombotic episodes. This leads to the conclusion that thrombosis in patients with anti-β_2-GPI antibodies can not be explained merely by the secondary β_2-GPI deficiency caused by circulating APL.[8]

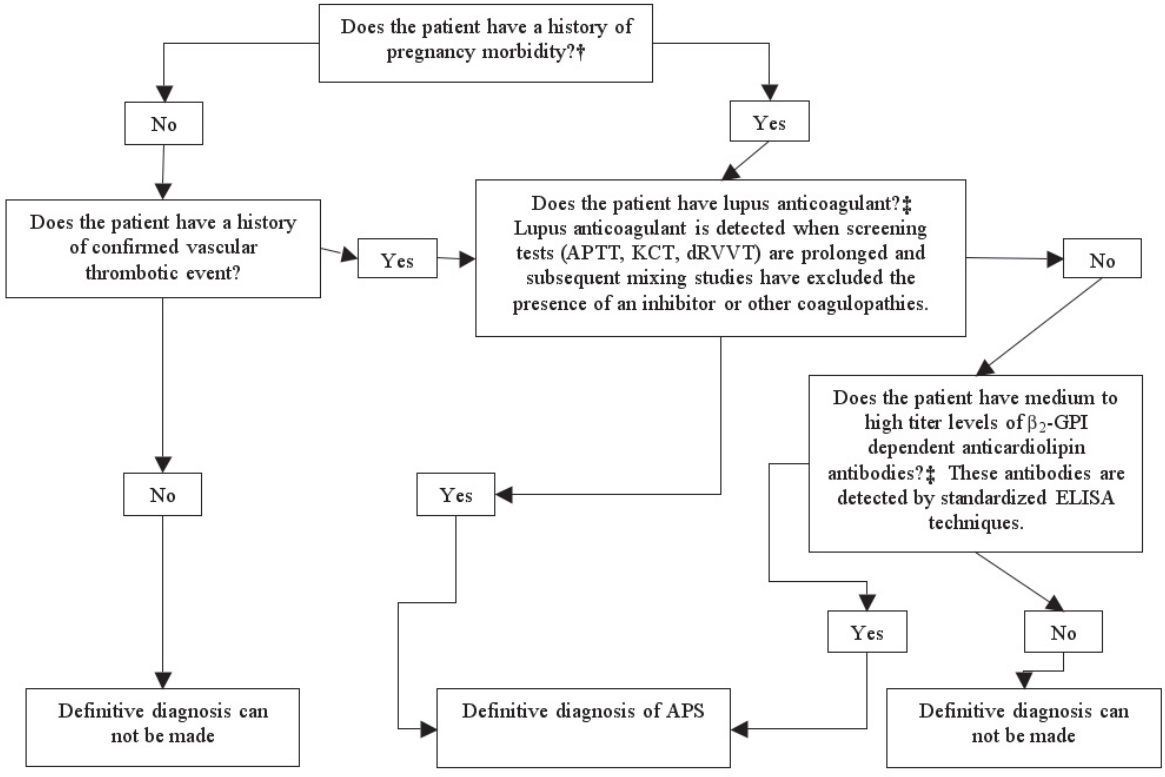
It is theorized that these antibodies bind cell surface phospholipids or phospholipid-binding proteins, thereby interfering with the clotting process or promoting it. Some of the proposed mechanisms of pathogenicity are stimulation of

platelet function, interference with the function of phospholipid-binding proteins, and activation of endothelial cells.[6] APL stimulate platelet function by binding to their phospholipid surface membranes. During platelet activation, there is an increase in exposure of anionic phospholipids on the external cell membrane, making them more reactive to APL and creating a repetitive cycle of activation and spontaneous aggregation.[1] β_2-GPI and annexin V are serum phospholipid-binding proteins that are believed to be naturally occurring circulating anticoagulants. Both bind endothelial cell surface anionic phospholipids rendering them unreactive for coagulation reactions. APL directed at these proteins interfere with their anticoagulant abilities and result in a procoagulant state. Activation of endothelial cells by APL causes upregulation of the expression of adhesion molecules (E-selectin, intracellular adhesion molecule-1 and vascular cell adhesion molecule-1) and secretion of cytokines (interleukin-1, and interleukin-6) promoting adhesion and inflammation.[1,6] Obstetric complications of APS include fetal death, pregnancy-induced hypertension, intrauterine-growth retardation and fetal heart block and are a result of thrombosis in the vasculature of the uterus and placenta.[5,9]

Clinical features

As previously stated, APS is characterized by arterial and venous thrombosis and consequently clinical features of the syndrome can vary widely and can involve any organ system. The features for both primary and secondary APS

Figure 1. Definitive diagnosis of APS*



* Modified from the "Criteria for the classification of definite antiphospholipid syndrome" [11]

† Pregnancy morbidity must fall in the following categories:

1. One or more unexplained death of a normal fetus at or beyond the tenth week of gestation
2. One or more premature births of a normal neonate before the thirty-fourth week of gestation due to severe preeclampsia or severe placental insufficiency
3. Three or more unexplained consecutive spontaneous abortions before the tenth week of gestation with parental chromosal and maternal anatomic or hormonal causes excluded

‡ Antibodies must be present on two occasions tested at least six weeks apart

are identical. Features involving the central nervous system most commonly include stroke, and less commonly cerebral dysfunction that can range from poor concentration or forgetfulness to severe dementia. The more important cardiac features of APS include manifestations of coronary artery disease (atherosclerosis and myocardial infarction) and valve disease which presents as vegetative masses and valvular wall thickening. Hypertension, present in 70% of patients, caused by renal and/or pulmonary involvement is a major clinical feature of APS. Manifestations that cause hypertension include pulmonary embolism, renal artery thrombosis and intrarenal vascular lesions. Skin features most frequently include livido reticularis, a purple-mottled fishnet pattern of the skin, and skin ulcers.

Mild to moderate thrombocytopenia, with platelet counts that range from 50-100 x 10^9/L, is present in 25% of APS patients but is rarely severe enough to cause bleeding. Other hematologic features include hemolytic anemia and a positive direct Coombs' test.[10] The primary and most significant obstetric complication is fetal loss occurring in the second and third trimester; however, it is not uncommon for the loss to occur in the first trimester.[5,9]

Diagnosis

Consensus criteria for the classification of definite APS were developed during the Eighth International APS Symposium held in Sapporo, Japan in 1998. Initially designed for selecting patients for research protocols, these criteria are commonly used for definitive diagnosis of APS. Keeping in mind that the criteria are not inclusive of all of the clinical manifestations known to occur in APS, a diagnosis can still be made if a patient demonstrates clinical features despite not meeting the criteria exactly. Definitive diagnosis is confirmed by the presentation of at least one clinical and one laboratory criterion as seen Figure 1.[11]

Laboratory testing

Laboratory diagnosis is based on detection of LA or moderate to high levels of IgG or IgM cardiolipin antibodies.[11] Results should be positive on two or more occasions, at least six weeks apart, because APL levels have been known to rise, fall, and even disappear.[5] Testing is indicated in all patients with spontaneous venous thrombosis, young patients (under 50 years) with stroke or arterial thrombosis, and in women with three or more consecutive pregnancy losses.[12]

It is recommended that LA be initially screened using tests such as modified activated partial thromboplastin time (APTT), kaolin clotting time (KCT), and dilute Russell's viper venom time (dRVVT). In vitro, LA interferes with the phospolipid dependent steps of coagulation thus producing prolonged results. If results are prolonged, mixing studies with normal plasma (APTT) and correction procedures (KCT, dRVVT) should be performed to determine whether the results are due to an inhibitor or factor deficiency.[12]

Anticardiolipin antibodies are detected using solid phase enzyme-linked immunosorbent assays (ELISA) coated with cardiolipin. These tests permit diagnosis of APS when LA is absent or if its presence can not be established (due to oral anticoagulation).[12] More specific testing, ELISA for the detection of β_2-GPI, may be required for a reliable diagnosis in the presence of infection or other diseases known to produce APL.[13] Retesting by a different laboratory may be indicated in patients with symptoms indicative of APS but who demonstrate negative or equivocal results because interlaboratory variation of test results can be high. One study undertaken to determine the variability of anticardiolipin assay results of 20 positive samples among ten laboratories revealed a mere 55% result concurrence. Their study results were found to mirror the results noted in the 2003 College of American Pathologists ACL-B survey for anticardiolipin antibody proficiency testing where an 80% consensus was reached for only five of the nine (55%) samples distributed for testing.[14]

Treatment and prognosis

Because it is not known if or when a thrombotic event will occur in patients with detectable levels of APL prophylaxis is not generally prescribed. Once a thrombotic event does occur, initial treatment with heparin followed by life-long oral anticoagulation with a target international normalized ratio (INR) of 3.0-3.5 is initiated.[12] Successful medical management relies on the prevention of future thrombosis. Pregnant women with APS are commonly treated with subcutaneous heparin because it does not cross the placenta. Low dose aspirin can also be used in addition to heparin up until the thirty-fourth week of gestation.[9]

Prognosis of APS is influenced by the severity and recurrence of thrombosis. Clinical manifestations of the syndrome that are associated with a poor prognosis include pulmonary or renal hypertension, cerebral ischemia, and myocardial infarction. If APS progresses to the "catastrophic" form, the prognosis is worse still. The catastrophic form of APS carries a mortality rate of 50% and most patients die from cardiac or respiratory failure.[15] Conversely, prognosis in pregnant

women can be favorable when treatment is started immediately upon pregnancy confirmation.

Summary

APS is a disorder that is characterized by the presence of APL, recurrent thrombosis, and fetal loss. It can occur in the absence of disease (primary APS) or in combination with other diseases (secondary APS). The exact pathogenic mechanism in which these antibodies cause thrombosis is not known; however, several hypotheses have been proposed such as activation of platelet and endothelial cells and interference with β_2-GPI. Clinical features of the syndrome may include stroke, livido reticularis, cardiac-valve disease, pulmonary embolism, thrombocytopenia, and hemolytic anemia. Diagnosis is based on the presence of at least one clinical and one laboratory criterion. Clinical criteria include one or more thromboses events in any organ, unexplained miscarriages at or before ten weeks of gestation, one or more premature births before 34 weeks of gestation, or three or more spontaneous abortions before ten weeks of gestation. Laboratory criteria include medium to high positive IgG or IgM anticardiolipin antibodies or detection of LA. Tests utilized to diagnose APS include coagulation assays (APTT, KCT, dRVVT) and ELISAs for the detection of cardiolipin and β_2-GPI antibodies. Unfortunately, the risk of thrombosis can not be predicted, and therefore treatment is not initiated until a thrombotic event occurs. Indefinite anticoagulation is prescribed once a thrombotic event occurs and anticoagulation therapy during gestation is prescribed to those with a history of recurrent spontaneous abortion. Prognosis primarily depends on the severity of the clinical manifestations. Some manifestations that confer a poor prognosis are pulmonary embolism and cerebral and myocardial ischemia.

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