

# 46 Antiphospholipid Syndrome

**Abstract:** Antiphospholipid antibodies (aPL) are a family of autoantibodies directed against phospholipids, phospholipid-binding proteins or both having a broad range of target specificities and affinities. Autoimmune aPL represents a spectrum of antibodies which includes biologic false-positive tests for syphilis (BFP-STs), LAC, and aCL. aCL is usually associated with presence of anti  $\beta_2$ GPI antibodies. Latter antibodies have been suggested to be more specific than aCL in predicting thrombosis. aPL have both procoagulant and anticoagulant effects. Various theories of pathogenesis of antiphospholipid syndrome (APS) are given in this article with clinical features and management.

Antiphospholipid antibodies (aPL) are a family of autoantibodies directed against phospholipids, phospholipid-binding proteins or both having a broad range of target specificities and affinities. Wasserman first described a type of aPL in 1906 associated with syphilis, labeled 'reagin', which was associated with false-positive serologic test for syphilis for various infections and collagen vascular diseases. The lupus anticoagulant (LAC) was described by Conley and Hartman which prolonged phospholipids-dependent coagulation steps *in vitro* by competing with coagulation factors for binding to phospholipids. In 1983, Hughes presented the concept of a syndrome of propensity for arterial/venous thrombosis, recurrent fetal loss of thrombocytopenia in some patients with systemic lupus erythematosus (SLE), this entity which was associated with aPL, anticardiolipin antibody (aCL), and LAC, was labeled as Hughes syndrome or antiphospholipid antibody syndrome.<sup>1,2</sup> In 1983, a solid phase immunoassay for anticardiolipin antibodies was developed which was strongly associated with LAC, false-positive VDRL test and thrombosis.<sup>3</sup> In 1990 the presence of  $\beta_2$  glycoprotein I ( $\beta_2$ GPI), which is a plasma phospholipids binding protein, was discovered. This protein is required by some aCL to bind to cardiolipin.<sup>4,5</sup>

## Immunology of Antiphospholipid Antibodies (aPL)

Autoimmune aPL represents a spectrum of antibodies which includes biologic false-positive tests for syphilis (BFP-STs), LAC, and aCL. About 80% of the patients have both LAC and aCL presence. Presence of anti- $\beta_2$  glycoprotein I antibody may be the most specific marker in predicting risk for complications in patients of aPL.<sup>6</sup>

There are three isotypes of aPL, namely IgM, IgG and IgA which are detected in autoimmune, infectious and drug-induced conditions. Autoimmune aPL is generally IgG<sub>2</sub> subclass and lambda light chain-predominant, have high avidity, and require the presence of  $\beta_2$ GPI. Infection-induced aPL is IgG<sub>1</sub> and IgG<sub>3</sub> subclass and kappa light chain-predominant, have low avidity and do not require  $\beta_2$ GPI.<sup>6</sup>

aCL is usually associated with presence of anti  $\beta_2$ GPI antibodies. Latter antibodies have been suggested to be more specific than aCL in predicting thrombosis.<sup>6</sup>

## Pathogenesis

Pathogenesis of thrombosis in aPL is ill-understood. aPL have both procoagulant and anticoagulant effects as shown in Table 1. Various postulations explaining the pathogenesis include:<sup>7</sup>

1. Activation of endothelial cells—Following the binding of aPL antibodies to endothelial cells there is upregulation of the expression of adhesion molecules, secretion of cytokines, and metabolism of prostacyclins.<sup>8</sup>
2. Oxidant-mediated injury of vascular endothelium-oxidized LDL activates macrophages leading to endothelial cell damage.<sup>9</sup>
3. aPL antibodies interfere with or modulate the function of phospholipids binding protein involved in the regulation of coagulation.<sup>10</sup>

Prothrombotic and proinflammatory properties of IgG-APS and IgM-APS are downregulated *in vivo* by an NF-kappa B inhibitor.<sup>11</sup> aPL induces significant increases in tissue factor (TF) transcription, function, and expression, in IL-6 and IL-8 up-regulation, and in inducible nitric oxide synthase (iNOS) expression on human umbilical vein ECs (HUVECs) and that these processes involve phosphorylation of p38 mitogen-activated protein kinase (MAPK) and activation of NF-kappa B. Understanding intracellular events in aPL-mediated EC activation may help in designing new targeted therapies for thrombosis in APS.<sup>12</sup>

*In vivo*, monocytes from primary APS patients have an increased expression of Vascular Endothelial Growth Factor (VEGF) and the tyrosine kinase Flt-1. Furthermore, *in vitro* results have indicated that this cytokine is produced by monocytes when treated with aPL, and that the p38 MAPK signalling pathway plays an important role. Thus, VEGF might act as a regulatory factor in aPL-mediated monocyte activation and TF expression, thereby contributing to the proinflammatory-prothrombotic phenotype of APS patients.<sup>13</sup>

Another study has shown that aPL induces TF expression in monocytes from APS patients by activating, simultaneously and independently, the phosphorylation of MEK-1/ERK proteins, and the p38 mitogen-activated protein kinases (MAP kinases)-dependent nuclear translocation and activation of NF-kappa B/Rel proteins.<sup>14</sup>

Some aCL bind to several serine proteases that participate in hemostasis and share homologous catalytic domains, demonstrating that some aCL in APS patients recognize one or more conformational epitopes shared by beta2GPI and the catalytic domains of disease-relevant serine proteases.<sup>15</sup>

The presence of antibodies against the complex of prothrombin and phosphatidylserine (aPS/PT) more significantly correlates with manifestations of Antiphospholipid Syndrome (APS) and with the presence of Lupus AntiCoagulants (LA) than antibodies against prothrombin bound to oxygenated polystyrene (aPT-A).<sup>16</sup>

Phosphatidylserine-dependent antiprothrombin antibody (aPS/PT) is more closely associated with manifestations of APS and LAC, and positive results from an aPS/PT test can mark thrombotic events in APS patients. The determination of aPS/PT in clinical practice, in conjunction with that of other aPL, may improve the likelihood of recognizing APS.<sup>17</sup>

Variable number of tandem repeats (VNTR) polymorphism of P-selectin glycoprotein ligand-1 (PSGL-1) is a significant determinant of thrombotic predisposition in patients with APS.<sup>18</sup>

Antibodies against beta2-glycoprotein I complexed with an oxidized lipoprotein relate to intima thickening of carotid arteries in primary antiphospholipid syndrome.<sup>19</sup>

**Table 1:** Effects of aPL on coagulation cascade

<i>Anticoagulant effect</i>	<i>Procoagulant effect</i>
Inhibition of activation of factor IX	Inhibition of the activated protein C pathway
Inhibition of activation of factor X	Inhibition of antithrombin III activity
Inhibition of activation of prothrombin to thrombin	Inhibition of anticoagulant activity of $\beta_2$ -glycoprotein I
Inhibition of fibrinolysis	
Activation of endothelial cells	

Enhanced platelet aggregation  
 Enhanced binding of  $\beta_2$ -glycoprotein I to membranes  
 Enhanced binding of prothrombin to membranes

**Table 2:** International consensus statement on preliminary criteria for the classification of the antiphospholipid syndrome\*

*Clinical criteria*

Vascular thrombosis

One or more clinical episodes of arterial, venous, or small-vessel thrombosis, occurring within any tissue or organ

Complications of pregnancy

One or more unexplained deaths of morphologically normal fetuses at or after the 10th week of gestation; or

One or more premature births of morphologically normal neonates at or before the 34th week of gestation; or

Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation

*Laboratory criteria*

Anticardiolipin antibodies

Anticardiolipin IgG or IgM antibodies present to moderate at high levels in the blood on two or more occasions at least six weeks apart

Lupus anticoagulant antibodies

Lupus anticoagulant antibodies detected in the blood on two or more occasions at least six weeks apart, according to the guidelines of the International Society on Thrombosis and Hemostasis

\*A diagnosis of definite antiphospholipid syndrome requires the presence of at least one of the clinical criteria and at least one of the laboratory criteria. No limits are placed on the interval between the clinical event and the positive laboratory findings.

**Table 3:** Laboratory detection of antiphospholipid antibodies

<i>Antibody</i>	<i>Method of detection</i>
Lupur anticoagulant (LAC)	<ol style="list-style-type: none"> <li>1. Prolongation of coagulation in at least one PL-dependant <i>in vitro</i> coagulation assay with platelet-poor assay               <ol style="list-style-type: none"> <li>a. Extrinsic pathway (dilute prothrombin time)</li> <li>b. Intrinsic pathway (activated partial thromboplastin time, kaolin clotting time)</li> <li>c. Final common pathway (Russell's viper venom time)</li> </ol> </li> <li>2. Failure to correct the prolonged coagulation time by adding normal plasma</li> <li>3. Normalization of clotting time by adding phospholipids or platelets. (This confirms presence of LAC)</li> <li>4. Rule out specific clotting factor deficiencies</li> </ol>
Anticardiolipin antibodies (aCL)	ELISA Significant levels Low positive : 10-20 GPL or MPL units Moderate positive : 20-80 GPL or MPL units* High positive : Above 80 GPL or MPL units*
Anti- $\beta_2$ Glycoprotein I	ELISA

\*(Moderate to high positive IgG anticardiolipin antibody assay present on more than one occasion at least 6 weeks apart is most specific for diagnosis of APS).

**Table 4:** Clinical manifestations in antiphospholipid syndrome

<i>Organ system</i>	<i>Manifestation</i>
Arterial	Thrombosis of the aorta
Cardiac	Angina, myocardial infarction, cardiac valvular vegetations, intracardiac thrombi, (Libman-Sacks endocarditis)
Cutaneous	Superficial thrombophlebitis, splinter hemorrhages, leg ulcers, livedo reticularis, superficial gangrene, purpura
Gastrointestinal	Budd-Chiari syndrome, hepatic infarction, intestinal infarction, splenic infarction, ischemic colitis, pancreatitis
Hematologic	Thrombocytopenia, hemolytic anemia, hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation
Miscellaneous	Avascular necrosis of bone
Neurologic	Transient ischemic attack, cerebrovascular accident, chorea, multi-infarct dementia
Obstetrical	Pregnancy loss, intrauterine growth retardation, HELLP syndrome
Ophthalmologic	Thrombosis of the retinal artery, thrombosis of the retinal vein
Pulmonary	Pulmonary emboli
Renal	Thrombosis of the renal vein, thrombosis of the renal artery, acute renal failure, chronic renal failure, proteinuria
Venous	Deep venous thrombosis of the legs

Enhanced FXIII activity may contribute to atherothrombosis in primary APS via increased fibrin/fibrinogen cross-linking. This pathway is not exclusive to primary APS, being present also in thrombotic controls, but the presence of IgG aPL may favor a higher degree of FXIIIa activation in the primary APS group.<sup>20</sup>

A considerable overlap of humoral immunity in rheumatic fever (RF) and APS, support a hypothesis that common pathogenic mechanisms underlie the development of cardiac valve lesions and central nervous system abnormalities in both diseases.<sup>21</sup>

The effects of aPL on coagulation cascade are shown in Table 1.

### **Criteria for Classification and Diagnosis**

The international consensus statement shown in Table 2 provides the criteria for the diagnosis of antiphospholipid syndrome.<sup>10</sup>

Antiphospholipid syndrome is divided into different categories. When it occurs in patients without clinical evidence of any other underlying autoimmune disease, it is labeled 'Primary', whereas one associated with autoimmune or other diseases is 'Secondary'. SLE is the most common associated condition with secondary antiphospholipid syndrome. Many conditions with aPL usually have IgM antibodies that are present at very low levels and are usually not associated with thrombotic events.<sup>23</sup>

### **Laboratory Detection of Antiphospholipid Antibodies**

Various laboratory methods used in detecting antiphospholipid antibodies are shown in Table 3.

### **Clinical Features**

Antiphospholipid syndrome presents with a diverse spectrum with involvement of almost any organ in the body. The clinical presentation largely depends upon the nature of size of the vessel involved and the temporal profile of thrombotic event. Table 4 for clinical manifestations in antiphospholipid syndrome.<sup>7,23</sup>

Deep vein thrombosis of legs is the common manifestation seen in 29 to 55% of patient.<sup>24-26</sup> Arterial thrombosis occurs commonly in the brain resulting in strokes and transient ischemic

attacks (TIAs) which account for 50% of arterial occlusion.<sup>24,27</sup> Coronary occlusions account for 23%, and remaining 27% involves subclavian, renal, retinal and pedal arteries.<sup>24</sup>

Valvular involvement occurs in 63% of patients which is detected on 2D-echocardiography. Systemic emboli can arise from mitral or aortic valve vegetations.

At times a clinical picture mimicking hemolytic-uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and other thrombotic microangiopathies may be seen following thrombosis in capillaries, arterioles or venules.<sup>7</sup> Other features include thrombocytopenia (40-50%), hemolytic anemia (14-23%), livedo reticularis (11-22%).<sup>24-26,28</sup> Renal involvement usually manifests with hypertension.

Obstetrical complications are an important feature associated with antiphospholipid antibodies. There is an unusually high proportion of pregnancy losses with fetal period (10 or more weeks of pregnancy).<sup>29,30</sup> High titers of IgG aPL and previous fetal loss are the two most sensitive predictors of fetal distress or death. Although aPL-related fetal loss is a more significant etiology in the second and third trimesters as many as 51% of aPL-associated losses may occur in the first trimester.<sup>6</sup> Placental microthrombosis and perturbation in a placental glycoprotein and a placental anticoagulant protein are the postulated pathogenetic mechanisms.<sup>6,23</sup>

Also, there is increased incidence of premature delivery due to pregnancy-associated hypertensive disease and uteroplacental insufficiency.<sup>31,32</sup>

## **Treatment**

Treatment of APS is three pronged, prophylaxis, prevention of recurrent thrombosis and treatment of acute thrombotic microangiopathy. Management of pregnancy in presence of aPL is an additional issue.

Aspirin<sup>33,34</sup> and hydroxychloroquin<sup>35</sup> are protective against thrombosis in APS. However, one study found no protective effect of aspirin in preventing DVT and pulmonary embolism.<sup>36</sup>

Anticoagulation decreases the rate of recurrent thrombosis. Warfarin is tried in different dosage to achieve the desired INR. It has been shown that INR of 1.9 or less does not confer significant protection.<sup>37</sup> INR of 3.0 or more carries a higher risk of bleeding.<sup>38</sup> Hence, an ideal INR of 2.0 to 2.9 should be achieved.<sup>38</sup> However, this still remains an unsolved issue. Aspirin alone is ineffective in reducing the rate of recurrent thrombosis.<sup>37,39</sup>

In the earliest detection of viable pregnancy, it is advisable to administer subcutaneous heparin (5000 units twice daily) alongwith low-dose aspirin.<sup>40,41</sup> This combination may promote successful embryonic implantation and protect against thrombosis of uteroplacental vasculature.<sup>42</sup>

Low molecular weight heparin may be substituted for standard heparin.<sup>43</sup>

Intravenous immunoglobulins have not been proved to be beneficial in pregnancy with APS.<sup>44</sup>

## **Catastrophic Antiphospholipid Syndrome**

Catastrophic antiphospholipid syndrome, a rarity, is defined by clinical involvement of at least three different organ systems over a period of days or weeks with histopathological evidence of multiple occlusions of large and small vessels.<sup>45</sup> These patients usually present with an acute thrombotic microangiopathy affecting small vessels of multiple organs;<sup>45</sup> viz. kidney (78%), lungs (66%), CNS (56%), heart (50%) and skin (50%). DIC which occurs in 25% of cases is a peculiar feature not seen in primary or secondary APS. Precipitating factors for catastrophic APS include infections, surgical procedures, withdrawal of anticoagulant therapy and use of oral contraceptives.<sup>45</sup>

This condition requires aggressive therapy with combination of anticoagulants and steroids plus either plasmapheresis or intravenous immunoglobulin.<sup>45</sup> Fibrinolytic agents streptokinase and urokinase have also been used to treat acute thrombotic microangiopathy.<sup>45,46</sup>

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