

# THE ANTIPHOSPHOLIPID SYNDROME

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## ABSTRACT

*The antiphospholipid syndrome (APS) describes an entity characterised by recurrent thrombosis, recurrent spontaneous abortions, thrombocytopenia, and elevated levels of antiphospholipid antibodies (IgG or IgM). The clinical features of APS include manifestations of thrombosis and/or cell damage. There is usually an associated underlying connective tissue disorder. The primary antiphospholipid syndrome refers to the presence of these clinical features without evidence of an associated autoimmune disorder. Detection of these antibodies include the lupus anticoagulant test, VDRL test and assays for anticardiolipin antibodies. Overlapping populations of these antibodies are detected by various immunologic tests. Management is based on the use of immunosuppressives, platelet inhibitors and anticoagulants.*

*Keywords: Anticardiolipin antibodies, antiphospholipid antibodies, thrombosis, foetal loss, thrombocytopenia.*

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## INTRODUCTION

Circulating lupus anticoagulant was first linked to thrombotic events by Bowie et al in 1963<sup>(1)</sup>. Interest in these antibodies was rekindled when a solid-phase immunoassay was developed by Harris and his colleagues in 1983<sup>(2)</sup>. This assay detects antibodies to cardiolipin (an anionic phospholipid) and hence the name anticardiolipin antibodies (ACA). Since then additional antibodies against phospholipids have been identified. The term antiphospholipid antibodies now encompass a spectrum of antibodies with different specificities against phospholipids which are associated with certain clinical features. In 1987, the "Antiphospholipid Syndrome or APS" was proposed by Harris et al<sup>(3)</sup> to describe a distinct clinical syndrome consisting of the following features: (a) venous and/or arterial thrombotic events, (b) recurrent spontaneous abortions, and (c) thrombocytopenia with antiphospholipid antibodies detected as significant titres (>5 SD) of IgG or IgM anticardiolipin antibodies or the lupus anticoagulant. Patients with antiphospholipid syndrome usually have a related autoimmune disease like SLE, Sjogren's syndrome, systemic sclerosis, although in some there is no underlying autoimmune disorder. The latter are now regarded as having the "Primary Antiphospholipid Syndrome".

## CLINICAL ASSOCIATIONS

The associated clinical features can be broadly classified as those due to thrombotic events eg strokes<sup>(4)</sup>, venous thrombosis<sup>(5)</sup> and those with cell damage eg autoimmune haemolytic anaemia<sup>(6,7)</sup>, immune thrombocytopenia<sup>(8,9)</sup>.

Other associated clinical features include livedo reticularis<sup>(10)</sup>, multistroke dementia<sup>(11)</sup>, chorea<sup>(12)</sup> and cardiac valve abnormalities<sup>(13,14)</sup>.

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## Thrombosis

Venous or arterial thrombosis correlate with an elevated IgG ACA level<sup>(15)</sup>. The thrombosis can affect a variety of blood vessels and reported cases include thrombosis of the deep leg veins, hepatic veins, retinal veins, superior and inferior vena cavae. Transient ischaemic attacks, strokes, thrombosis of the aorta, femoral and visceral arteries have also been documented. Association of ACA with a subgroup of myocardial infarction patients have been noted<sup>(16)</sup> but not confirmed by other groups. In patients with SLE and pulmonary hypertension, the association with antiphospholipid antibodies may indicate past episodes of pulmonary emboli or intrapulmonary thrombosis<sup>(17)</sup>.

## Recurrent Foetal Loss

Recurrent foetal loss have been shown to correlate with the presence of IgG ACA<sup>(18,20)</sup> and one study showed the presence of thrombi in the aborted placenta<sup>(21)</sup> suggesting that placental thrombosis and infarction may play a role in the pregnancy loss. The foetal loss is also noted to occur relatively later in pregnancy (about 17 weeks)<sup>(22)</sup>.

## Immune Cytopenias

Elevated levels of different ACA subtypes are found in immune cytopenia like autoimmune haemolytic anaemia in SLE<sup>(23,24)</sup> and immune thrombocytopenia<sup>(25)</sup>. The former correlate with elevated IgM ACA levels while the latter is associated mainly with IgG ACA levels.

## THE PATHOGENETIC ROLE OF ANTIPHOSPHOLIPID ANTIBODIES

The role of these antibodies has not been definitely settled. There is some evidence of a pathogenic role of these antibodies in the thrombotic process. The actual mechanism is not known. One of the proposed mechanisms is the effect of these antibodies on the vascular endothelium in blocking the release of arachidonic acid and thus causing a decreased production of prostacyclin, and leading to increased platelet aggregation, ultimately cumulating in a thrombotic tendency<sup>(26)</sup>. Other hypotheses include the interference of these antibodies with the function of protein C in the degradation of clotting factors resulting in an enhancement of clotting<sup>(27)</sup>, the binding of these antibodies to a complex antigen that contains beta<sub>2</sub> glycoprotein I (apolipoprotein H), an inhibitor of the intrinsic coagulation pathway, leading to a thrombotic predisposition<sup>(28)</sup>.

The role of these antibodies in cytopenias is far less well defined than that of thrombosis. It has been suggested that the binding of these antibodies to phospholipids in platelet membrane can lead to platelet activation and aggregation<sup>(29)</sup> thus leading possibly to thrombocytopenia. In addition, this process might also enhance platelet destruction by the reticuloendothelial system causing further cytopenia. A similar mechanism may occur in immune haemolytic anaemia.

#### DETECTION OF ANTIPHOSPHOLIPID ANTIBODIES

The first antiphospholipid antibody to be detected is the lupus anticoagulant, demonstrated by a prolongation of the partial thromboplastin time (PTT) or kaolin clotting time (KCT), and not correctable by the addition of normal plasma<sup>(30)</sup>. The subsequent development of a sensitive ELISA method using cardiolipin as antigen to detect anticardiolipin antibodies gave a boost to the routine detection of these antibodies. In addition it enabled the detection of ACA isotypes (IgG, IgM, IgA). However certain points need to be borne in mind. Studies using affinity purified ACA show that a plasma protein co-factor is necessary for binding to liposomes and characterisation of this co-factor show that it closely resembles beta<sub>2</sub>-glycoprotein I (apolipoprotein H)<sup>(31)</sup>. Heat treatment of antiphospholipid antibody-negative serum or plasma samples for as short as 30 min at 56°C to inactivate complement activity can cause a false positive result<sup>(32)</sup>. The Venereal Disease Reference Laboratory (VDRL) test is another serological test for the presence of antiphospholipid antibodies. This test contains both cardiolipin and phosphatidylcholine as antigens. This is a biological false-positive result because all these patients gave negative results when tested with more specific tests for syphilis eg Treponema Pallidum Haemagglutination test (TPHA). There are reported correlations between different populations of antibodies assayed by the various laboratory tests but not total concordance, thus indicating the existence of overlapping groups of antibodies.

#### MANAGEMENT OF APS

The present medical management of the antiphospholipid syndrome consists of the use of immunosuppressives, platelet inhibitors and anticoagulants, singly or in combination. The basis for using corticosteroids is to suppress antiphospholipid antibody activity<sup>(33)</sup>. However there is no convincing evidence that this is actually the case as ACA levels can remain high despite high dose corticosteroid treatment<sup>(34)</sup>. The optimal dose of corticosteroids to be used is unknown although a daily dose of 40 mg to 60 mg of prednisolone has been recommended for recurrent aborters ie those with more than two spontaneous abortions<sup>(35)</sup>. The potential benefits of such a therapy may not outweigh the potential side effects of pre-eclampsia, foetal growth retardation and prematurity. The heightened awareness of the role that ACA play in recurrent aborters has resulted in more careful ante-natal care and regular foetal monitoring. These factors contribute significantly to successful pregnancies.

Low dose aspirin can selectively inhibit thromboxane A<sub>2</sub> synthesis and theoretically can prevent occlusion of small vessels. Subcutaneous heparin have been used successfully in recurrent aborters<sup>(36)</sup>. However the use of low dose aspirin and subcutaneous low molecular weight heparin as a standard treatment for recurrent spontaneous abortions is still the subject of ongoing therapeutic trials.

Long term anticoagulation with warfarin in patients with high levels of these antibodies and a history of recurrent strokes or venous thrombosis has been proposed by some<sup>(37)</sup>. The use of anti-platelet agents has not been proven to be definitely effective in treating the cerebrovascular features of this syndrome. In addition, corticosteroids use did not pre-

vent recurrences of stroke or the onset of multistroke dementia and its use should be limited to those with an associated connective tissue disorder.

Hydroxychloroquine has been shown to have an inhibitory effect on phospholipase A<sub>2</sub> and therefore can affect platelet adhesion. One study suggested that hydroxychloroquine may prevent thromboembolic events<sup>(38)</sup>. It is therefore a potentially useful drug and controlled trials are needed to delineate its efficacy.

Ongoing controlled clinical trials and basic research into the underlying pathophysiology of the antiphospholipid antibodies promise more answers in the management of this fascinating condition.

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