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Anticardiolipin syndrome: antiphospholipid syndrome

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Anticardiolipin syndrome, more appropriately called antiphospholipid syndrome (APS), is an autoimmune disorder characterised by recurrent venous or arterial thrombosis, fetal loss, thrombocytopenia, and some other clinical complications associated with antiphospholipid (aPL) antibodies[1] (Table 1). Some components of this syndrome have been known since the 1950s, but the whole syndrome was recognised in 1983 when simple and reproducible methods for the detection of aPL antibodies became available[2–4].

Epidemiology

APS was first described in patients with systemic lupus erythematosus (SLE) (secondary APS), but it may occur in the absence of any other disorder (primary APS). Major clinical features are similar in both forms. The syndrome has been reported in all ethnic groups, but seems to be both less common and less severe among patients from the Indian subcontinent and in African Americans and African Jamaicans. It was first described in adults, but is also found in children. The female to male ratio is 6:1.

Pathogenesis

The close association of aPL antibodies with thrombosis and pregnancy loss strongly suggests these antibodies have a causative role. This is supported by induction of these complications in normal mice following passive transfer of aPL antibodies from APS patients[5,6]. Several mechanisms by which aPL antibodies may cause these complications have been suggested:

- Activation of endothelial cells and increased expression of adhesion molecules, resulting in increased adherence of platelets and monocytes to endothelial cells.
- Alteration of prostacyclin/thromboxane balance.
- Impairment of antithrombin III activity via cross-reactivity with glycosaminoglycans.
- Inhibition of thrombomodulin protein C-protein S activation.

Key Points

Antiphospholipid syndrome (APS) is defined as recurrent thrombosis or recurrent fetal death associated with anticardiolipid (aCL) or lupus anticoagulant (LA) antibodies

APS may occur in the absence of systemic lupus erythematosus (SLE) or any other autoimmune disorder

Untreated thrombosis in APS has a high risk of recurrence, unless long term aggressive anticoagulation is administered

Anticoagulation for thrombosis in APS may need to be continued for life

A pregnant woman with a past history of pregnancy loss, and high levels of IgC aCL antibodies without treatment, has a very high risk of pregnancy loss

Catastrophic APS has a mortality rate of over 50% and may be triggered by discontinuation of anticoagulation, by surgery or by infection

- Interference with the function of other coagulation inhibitors (eg β_2-glycoprotein I (β_2GPI) and annexins V).

Clinical features

Patients with APS may have recurrence of one complication or episodes of several different complications: for example, a woman with recurrent fetal loss may develop deep vein thrombosis or thrombocytopenia.

Thrombosis

The majority of clinical manifestations of APS appear to be caused by thrombosis or thromboembolic vascular occlusions. Histological studies do not show vasculitis. There may be some cellular infiltration, but never destruction of the vessel wall. Veins and arteries of all sizes and at any location may be involved. Thrombosis is recurrent; it may be confined to a single location or may occur at different sites, in the arterial as well as the venous circulation. Clinical locations of APS-associated venous and arterial thrombosis are shown in Table 2.

Catastrophic antiphospholipid syndrome

Patients with aPL may develop widespread thrombosis in multiple organs over a period of days to weeks. This condition is often caused by discontinuation of anticoagulation, by surgery or by infection. The patients are often extremely ill, with multiple organ failure and rapidly declining mental status[7]. Mortality is over 50%.

Recurrent pregnancy loss

Recurrent spontaneous abortion is a frequent complication of APS[8]. The rate of fetal death in women with SLE and immunoglobulin (Ig) G aPL antibody is up to six times higher than in healthy women. Moreover, a history of prior fetal losses in women with high levels of aPL compounds the risk for further fetal demise. Fetal death during the second or third trimesters is more specific for aPL-associated fetal loss, but first trimester spontaneous abortion is not uncommon. Placental insufficiency due to thrombosis is believed to cause fetal growth retardation, fetal demise and preterm labour. There have been reports of thrombosis occurring in neonates of mothers with APS, but the risk of these children developing APS is small, and the major long-term complications are more likely to be secondary to their low birth weight.

Table 1. Clinical and laboratory features of antiphospholipid syndrome.

Clinical features	Laboratory features
Main features: venous thrombosis arterial thrombosis recurrent fetal wastage or death thrombocytopenia	anticardiolipin antibodies (medium to high) positive IgG, IgM or IgA
Other features: livedo reticularis stroke in young persons (<50 years) myocardial infarction in young persons (<50 years) endothelial vegetation cardiac valve lesions transverse myelopathy chorea migraine-like headache leg ulcers	lupus anticoagulant (confirmed by mixing and neutralisation)

Ig = immunoglobulin.

Table 2. Venous and arterial thrombosis associated with antiphospholipid syndrome.

Site of thrombosis	Clinical symptoms
Venous:	
renal vein	proteinuria
hepatic vein	Budd-Chiari syndrome
portal vein	portal hypertension
mesenteric vein	acute abdomen
venacaval thrombosis	enlarged liver, generalised oedema
deep vein thrombosis	
axillary vein	
Small veins:	
adrenal veins	Addison syndrome
central retinal vein	loss of vision
Arterial:	
pulmonary emboli	pulmonary hypertension
cerebral arteries	stroke, transient ischaemic attack, multi-infarct dementia
coronary arteries	myocardial infarction
thoracic aorta	aortic arch syndrome
abdominal aorta	bowel infarction
lower abdominal aorta	ischaemic claudication
peripheral arteries	gangrene
Small arteries:	
adrenal arteries	Addison syndrome
retinal (ophthalmic) artery	loss of vision
dermal arteries	dermal gangrene
digital arteries	digital gangrene

Neurological complications

Stroke and transient ischaemic attacks are the most common neurological complications associated with APS. Other complications include transverse myelopathy, chorea, seizures and migrainous headache[9].

Thrombocytopenia and haemolytic anaemia

Thrombocytopenia in APS is usually mild (>50,000 platelets/mm^3) and may be associated with Coomb's-positive haemolytic anaemia (Evans syndrome).

Cardiac complications

Cardiac abnormalities in APS patients may present as ischaemia or infarction of the left, or occasionally the right, ventricle secondary to coronary artery thrombosis. Cardiac valve lesions, endocardial vegetations or pseudotumours have been reported.

Cutaneous lesions

Livedo reticularis, leg ulcers, digital gangrene and widespread cutaneous necrosis are recognised features of APS.

Antiphospholipid antibodies

Biologically false positive serological tests for syphilis. Historically these antibodies were detected as biologically false positive serological test for syphilis (BFP-STS). When the Wasserman reaction or the Venereal Disease Research Laboratory (VDRL) test was positive but the specific tests for *Treponema pallidum* were negative, the reaction was called FBS-STS. Association of this reaction with SLE and some other autoimmune conditions has been known since the early 1950s. These tests are not used for the diagnosis of APS due to lack of sensitivity.

Lupus anticoagulant antibodies (LA). These antibodies compete with clotting factors in binding to anionic phospholipid (PL) and prolong the PL-dependent steps of the coagulation cascade (eg activation of factor X and conversion of prothrombin to thrombin). They are detected by clotting tests such as the kaolin clotting test (KCT), the activated partial thromboplastin time (APTT) and dilute Russell viper venom time (dRVVT). These tests require fresh platelet-depleted plasma. To rule out clotting factor deficiencies, all positive LA tests need to be confirmed by mixing with normal freeze thawed platelet or PL preparations, but not with normal plasma. The antiphospholipid nature of LA and the paradoxical association with thrombosis were recognised in 1957.

Anticardiolipin antibodies (aCL). These antibodies are detected by ELISA using microtitre plates coated with cardiolipin in ethanol. Test sera are diluted in 10% bovine serum in phosphate buffered saline[3]. This assay has been standardised, and international calibrators for the test and units for the antibody have been developed[10]. Large numbers of sera were tested, and a statistically significant association of these antibodies was detected with recurrent thrombosis, recurrent abortion, thrombocytopenia and positive LA test, and the anticardiolipin syndrome was described[4]. Other anionic PL, such as phosphatidylserine and phosphatidylinositol, have been used as antigens in this assay. Antibodies to other PL have also been detected. A high degree of cross-reactivity between antibodies to different anionic PL has been found, suggesting that all these antibodies are directed against epitopes shared among anionic PL. The term 'anticardiolipin' was therefore changed to 'antiphospholipid' to include all these antibodies, and the syndrome is often called the 'antiphospholipid syndrome'.

Antiphospholipid cofactor: β_2-glycoprotein I

In 1990, the autoimmune disease-associated antibodies were reported to require a cofactor for binding to PL[11–13]. This cofactor was identified as β_2GPI, a normal plasma protein that binds anionic PL and is believed to be a regulator of coagulation. It is controversial whether aPL binds epitopes formed jointly by PL and or cryptic epitopes on β_2GPI being exposed after binding to PL. In any case, in aCL, ELISA bovine serum in sample buffer provides enough to form or expose the epitopes for aPL binding.

Diagnosis

Based on the 1998 consensus workshop[14], APS is now diagnosed if at least one of the clinical criteria and one of the laboratory criteria are met.

Clinical criteria

- Vascular thrombosis
- Pregnancy morbidity (fetal wastage or death).

Laboratory criteria

The laboratory criteria, which must be positive on two or more tests at least six weeks apart, are aCL and LA antibodies. Familial deficiencies of protein C, protein S, or antithrombin III, and factor V resistance to protein C (factor V Leiden) should be looked for.

Treatment of antiphospholipid syndrome

- *Antiphospholipid antibodies* with no clinical complications do not need any treatment, but must be carefully followed. Some clinicians give small doses of aspirin (70 mg).
- *Thrombocytopenia* is treated with prednisone.
- *Thrombosis* in APS requires heparin, followed by oral anticoagulant (warfarin). Anticoagulation should be continued indefinitely, with adequate doses of anticoagulant to achieve an international normalised ratio of 3–3.5 to diminish the risk of recurrence[15].
- *Catastrophic APS:* intravenous (IV) heparin, IV corticosteroid and IV cyclophosphamide, as well as plasmapheresis should be tried.
- *Pregnancy loss:* the treatment remains controversial, in particular the use of steroids in the prevention

of fetal loss. There is evidence favouring the use of aspirin and heparin throughout the gestation period to prevent abortion[16]. Low-molecular weight heparin has also been successfully used. Recently, high-dose IV Ig has been used with some success.

Prognosis

In a 10-year follow-up of 52 patients with high aCL antibodies[17], 31 of whom already had clinical complications, 29% experienced further thrombosis, 52% of those with no clinical complications developed thrombosis during the follow-up period, and five patients (10%) died.

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