Antiphospholipid Syndrome - Clinical overview

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Antiphospholipid antibody syndrome (APS), a non-inflammatory autoimmune disorder, is now recognized as one of the commonest cause of acquired thrombosis. It is characterized clinically by recurrent arterial and venous thrombosis (in contrast to other prothrombotic states like protein C, protein S, AT III deficiency where only venous thrombosis is the feature), adverse pregnancy outcome and/or thrombocytopenia in association with sustained high titres of antiphospholipid antibodies (aPL). Antiphospholipid antibodies are found in a wide variety of states and may be asymptomatic or associated with a diverse spectrum of clinical manifestations. The incidence of antiphospholipid antibodies increases with age and may be identified in up to 14% of healthy elderly people and in up to 50% of SLE patients. The presence of these antibodies in the absence of a clinical event does not warrant any treatment. Some studies have revealed an increased incidence of HLA-DR4, DR7, DRW53 associated with the syndrome. Triggers for the development of the syndrome or determinants for location of thrombosis have not yet been elucidated.

aPL antibodies are a heterogeneous group of antibodies with different characteristics and clinical associations. In 1941 Pangborn isolated antigenic component from bovine heart extracts as a lipid, cardiolipin. This was the major component of VDRL test. It is recognized that a large number of individuals whose sera were positive for VDRL did not have signs of syphilis (biologic false positive serologic test for syphilis BFP-STS). Moore and Mohr identified two patterns of BFP-STS (a) acute and transient pattern seen in relation to infections (b) chronic pattern with positivity lasting for more than 6 months were found to have high prevalence of autoimmune disease like SLE. Later lupus anticoagulant (LA) was identified and its paradoxical association with thrombosis was reported.

APS has been recognized largely as a disease of young women due to its association with SLE and pregnancy loss.

The age of first thrombosis in APS has been shown to be predominantly between 30 and 45 years.

An international consensus statement on classification criteria for definite APS was published after a workshop in 1998, and amended in 1999.5

Clinical Criteria

1. Vascular thrombosis:
   One or more clinical episodes of arterial, venous, small vessel thrombosis in any tissue or organ.

2. Pregnancy morbidity:
   a. One or more unexplained death of a morphologically normal foetus at or beyond the 10th week of gestation.
   b. One or more premature births of morphologically normal neonates at or before 34th week of gestation.
   c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and paternal and material chromosomal causes excluded.
   d. Adverse pregnancy outcome without history of foetal loss.

Laboratory Criteria

1. Anticardiolipin antibody (aCL) of IgG and/or IgM isotype in blood, present in medium or high titre, on two or more occasions at least 6 weeks apart, measured by a standard ELISA for β2 glycoprotein 1-dependent antiphospholipid antibodies.

2. Lupus anticoagulant (LA) present in plasma on two or more occasions at least 6 weeks apart.

Definite APS is considered to be present if at least one of the clinical and one of the laboratory criteria are met.

Clinical Features

Thrombosis

Arterial or venous thrombosis is one of the major features of the syndrome. aPL should be included in the work-up of unexplained thrombosis particularly in unusual sites or in young patients. The commonest site of venous thrombosis is the large veins of the lower limbs. Arterial thrombosis particularly affecting the cerebral circulation is being increasingly recognized. In 1993 antiphospholipid antibodies in stroke study evaluated 255 consecutive first ischaemic stroke patients and 255 matched controls for the presence of aCL as an independent risk factor for stroke. The prevalence of aCL in the stroke group was 9.7% compared with 4.3% in the controls. An odds ratio of 2.3 after adjustment for other known risk factors for ischaemic events was determined. None of the patients had SLE.

In acute myocardial infarction (AMI) the prevalence of aCL is between 5% and 15%.

A major focus of research is identifying risk factors of thrombosis so that we can identify those that require more aggressive treatment. At this stage, the best predictor appears to be previous thrombotic history, LA and high titres of aCL.
Cutaneous disease
The hallmark of cutaneous lesion is livedo reticularis. It is characterized by a mottled, purple, reticular pattern with different localization, extension, infiltration and regularity of fishnet pattern.

Skin ulcers are also common in APS. Thrombosis of the small vessels with vascular proliferation and minimal inflammatory changes are found.

Neurologic
Association with stroke has already been described. There are several reports of cerebral dysfunction in APS, ranging from mild cognitive dysfunction to severe dementia. The more severe associations include dementia, psychosis, myelopathy, MS-like syndrome, chorea, sensorineural hearing loss, cerebral artery or vein occlusion and retinal lesion. Although the pathologic lesion is likely to be thrombotic, there is some evidence for direct neurotoxicity. Two recent studies have found that psychomotor function in SLE was reduced in patients who had persistently positive IgG aCL antibody.

Heart
The most important cardiac manifestations are valve disease, coronary artery disease (CAD) and less commonly cardiomyopathy and intracardiac thrombus.

Valve disease is present in around 48% of patients with SLE and aPL and in only 21% of SLE patients negative for aPL. Two morphologic echocardiographic patterns can be discerned. The predominant functional abnormality is regurgitation, whereas stenosis is rarely seen. The mitral valve is the most commonly affected site.

CAD has been documented in APS patients. Around 35% of SLE patients are positive for aPL and the contribution of aPL to the development of AMI in this population may indeed be substantial. Whether aCL contributes to the development of coronary heart disease or appears later as a consequence of myocardial injury is still uncertain.

Renal
Renal involvement is a prominent feature in APS. Amigo et al (1992) found renal involvement in up to 25% of patients with primary APS. Hypertension is the most common clinical manifestation being present in more than 70% of patients. It may be pathogenetically related to thrombosis in a renal artery and intrarenal vascular lesion. All hypertensive patients with antiphospholipid antibody should be evaluated for renal artery stenosis. The renal involvement is usually chronic in APS. In patients with primary APS the observed outcome of renal transplant is worse.

Lung
The commonest pulmonary manifestations include pulmonary embolism and thromboembolic pulmonary hypertension.

Haematologic
Thrombocytopenia has been found in up to 30% of APS and is seen more frequently in SLE with aPL. Despite thrombocytopenia, some patients are still at risk of thrombosis. Coomb’s positive hemolytic anaemia may also occur (14% in primary APS and 40% in APS to secondary SLE).

Pregnancy
Pregnant women with APS are at high risk of maternal and foetal pregnancy related complications.

The association between aPL and recurrent miscarriage is well known, with second trimester loss being particularly common. An exceptionally high rate of pre-eclampsia has been reported in women with APS, which contributes to the high rate of pre-term delivery in this condition. 15% of women with a history of three or more consecutive miscarriages have persistently positive aPL results. The risk of pregnancy loss is directly related to antibody titre, particularly IgG aCL. Progressive thrombosis of placental microvasculature leads to infarction causing placental insufficiency.

Catastrophic APS
This is a rare fulminant form of APS characterized by acute multiorgan system deterioration caused by widespread thrombosis of small and large vessels. Renal involvement was noted in 70%. Hypertension and pulmonary disease like ARDS, pulmonary embolism were also common, CNS involvement occurred in 56% with confusion, disorientation and stupor. Cutaneous manifestations in the form of livedo, tender nodules, digital ischaemia, ischaemic ulceration and splinter haemorrhages have also been documented. Gastrointestinal ischaemia was seen in 38%. Thrombocytopenia was noted in 68%, 26% had haemolytic anaemia and 28% had evidence of DIC. Death occurred in 50%. A minority of the patients demonstrated large vessel occlusion in contrast to simple APS. The clinical presentation may mimic TTP, acute DIC which can be differentiated by laboratory finding.

TREATMENT

General measures
Lifestyle measures including reduction of risk factors are important. Combined oral contraceptive pills are to be avoided.

Asymptomatic patients
Elevated titre of antiphospholipid antibodies in a healthy person does not warrant systemic anticoagulation. Many physicians recommend low dose aspirin for management of these patients even without previous thrombosis, particularly if titres of aPL are high. However, there is little objective evidence to support this view.

Thrombotic events
Arterial and venous thrombosis are treated with heparin (LMWH or UFH) followed by oral anticoagulants like warfarin (maintaining INR ≥ 3). The current recommendation is that anticoagulation should be lifelong, given the risk of recurrent events.

Treatment of catastrophic APS has involved glucocorticoids, cyclophosphamide, plasmapheresis, IV immunoglobulin, anticoagulation and in occasional patients thrombolytic therapy.

Mild to moderate thrombocytopenia (70,000-150,000/mm³) has been shown to improve with low dose aspirin (80-150 mg/day). Anticoagulation may be continued even when platelet count is below 50,000/mm³ as the patient nevertheless remains at risk of thrombosis. In severe thrombocytopenia, glucocorticoids and intravenous immunoglobulin (IVIG) are usually effective. Monoclonal antibody therapy with anti CD40 ligand may be an option in the future. There is some debate as to the effectiveness of splenectomy in APS.

A frequent problem is the management of menorrhagia specially when INR is maintained at high levels. “Mirena”
coil, an intrauterine coil with a silastic capsule containing levonorgesterol has been found to be helpful.

The management of pregnancy in women with APS is the subject of much debate. Antithrombotic treatment is preferred to glucocorticoids. Whether adding heparin to low dose aspirin in women with recurrent miscarriage, but without a history of thrombosis, improves foetal outcome over and above low dose aspirin alone is controversial. Two recent studies have suggested that low dose aspirin and heparin can improve the live birth rate from 40 to 80% in women with a history of first trimester recurrent miscarriage. Closer obstetric surveillance is the most important factor for improved outcome. For patients who continue to have pregnancy losses despite heparin and low dose aspirin and IVIG may be an option. Anticoagulation should be continued for 3 months after delivery as peripartum and post-partum thrombotic events have been reported.

REFERENCES