

Antiphospholipid antibody syndrome (APS) is an acquired prothrombotic state characterized by the presence of one of the clinical criteria of either vascular thrombosis in the arterial or venous tree and recurrent pregnancy losses; supported by the laboratory criteria of presence of antiphospholipid antibodies namely anticardiolipin antibody (ACLA), lupus anticoagulant (LAC) or β_2 glycoprotein I (β_2 GPI) antibody. It is also called as Hughes syndrome. Table 1 gives the revised Sapporo classification criteria for APS. The term APS is not synonymous with antiphospholipid antibody (APLA). There can be presence of the circulating APLA without any clinical manifestations. The presence of APLA may not always mandate therapy whereas APS mandates treatment.

Antiphospholipid antibodies (APLA) are directed against phosphatidyl choline, phosphatidyl serine, phosphatidyl glycerol and phosphatidyl ethanolamine. Anticardiolipin antibody is directed against diphosphatidyl glycerol.

Table 1: Revised Sapporo Classification Criteria for APS

• **Clinical Criteria**

1. Vascular thrombosis

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

2. Pregnancy morbidity

- a. One or more unexplained deaths of a morphologically normal fetus at or beyond 10th week of gestation
- b. One or more premature births of a morphologically normal neonate before 34th wk of gestation because of recognized features of placental insufficiency or
- c. 3 or more unexplained consecutive spontaneous abortions before 10th wk of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

• **Laboratory Criteria**

1. Lupus Anticoagulant present in plasma
2. Anticardiolipin antibody of IgG or IgM isotype in serum or plasma, present in medium or high titre (> 40GPL or MPL or more than 99th percentile) by ELISA
3. Anti β_2 glycoprotein I antibody of IgG or IgM isotype in serum or plasma (in titre > 99th percentile) by ELISA

(detection of 1 of the above antibodies on 2 or more occasions at least 12 wk apart)

ACLA causes more arterial thrombosis whereas LAC causes more venous thrombosis. APLA may be detected even in healthy individuals, advancing age, lymphoproliferative diseases, syphilis, HIV, Lyme disease, infectious mononucleosis, tuberculosis, certain drugs like phenytoin, valproate, phenothiazines, procainamide, chlorpromazine and hydralazine.

APS can be primary or secondary. Secondary APS is seen in conditions like SLE, RA, autoimmune hypothyroidism, malignancies, HIV and drugs. SLE is the most common rheumatological condition associated with secondary APS. In all patients of SLE with systemic involvement, there is a high association with APS. Hence, it is recommended to screen these patients with APLA. However, in cases of cutaneous lupus without systemic involvement, this screening is not recommended.

PATHOGENESIS

The exact role of the antibodies in the pathogenesis of thromboembolism is not clearly understood. Following mechanisms are the most accepted ones:

1. It is postulated that endothelium, platelets, trophoblasts, prothrombin, activated protein C, annexin-V, antithrombin 3 and tissue factor have a definite role in the pathogenesis of thrombosis. The activation or apoptosis of these cells causes migration of negatively charged phospholipids to the outer cell membrane, which otherwise is electrically neutral. β_2 GPI binds to these negatively charged phospholipids which in turn forms a complex (dimer). This complex activates complement cascade which favours proinflammatory mediators which induce the process of thrombosis.
2. The oxidant-mediated damage to vascular endothelium by APLA.
3. By interference or modulation of phospholipid binding proteins which are involved in the regulation of normal coagulation pathway; the procoagulant effect is exerted by APLA.

CLINICAL FEATURES

Thromboembolic phenomena can occur anywhere in the vascular tree. Hence, the clinical features of APS can be seen in any part of the body. The commonest manifestations according to the system involved are mentioned below.

- I. Central Nervous System: Young stroke presenting

Table 2: Differential diagnosis of CAPS

Factor V Leiden mutation
Hyperhomocysteinaemia
Vasculitis e.g. Classical Polyarteritis nodosa
Infective Endocarditis with embolic phenomena
Thrombotic thrombocytopenic purpura (TTP)
Cholesterol embolism
Malignancy
Hemolytic Uremic syndrome (HUS)
Sepsis
Disseminated Intravascular Coagulation (DIC)

as hemiplegia, cortical sinus thrombosis presenting as paraparesis or seizures, multi-infarct dementia, migraine headache, Guillain Barre syndrome, chorea and optic neuritis.

- II. Obstetrics: Recurrent foetal losses usually after 10th week of gestation, early eclampsia, HELLP syndrome, IUGR, IUFD, thrombocytopenia. Placental vessel thrombosis causing poor placental perfusion is the cause of these symptoms. Normally, Annexin V has anticoagulant activity. This annexin V is reduced on placental villi in APS, which favours a procoagulant state and therefore thrombosis.
- III. Renal: Proteinuria, hematuria, nephritic syndrome, severe hypertension, renal vein thrombosis, renal failure or end stage renal disease are the manifestations.
- IV. Cardiac: Valvular thickening, valvular regurgitation, stenosis, myocardial infarction, intracardiac emboli. Sometimes, a patient may need valve replacement surgery.
- V. Pulmonary: Pulmonary embolism, chronic pulmonary thromboembolism, ARDS, intra-alveolar hemorrhages and pulmonary hypertension.
- VI. Skin: Livedo reticularis, ulcerations, digital gangrene, subungual splinter hemorrhages, superficial thrombophlebitis and deep vein thrombosis (DVT). Skin manifestations are commonly seen in CAPS.
- VII. ENT: Autoimmune sensorineural hearing loss presenting as bilateral progressive deafness may be one of the rarer symptoms of APS.

CATASTROPHIC APS (CAPS)

It is one of the rheumatological emergencies which is life-threatening. It can present as multiorgan failure. Kidney is the most commonly affected organ in CAPS followed by lungs, CNS, heart, adrenals and skin. The clinical presentation consists of stroke, respiratory failure, deranged liver and renal functions requiring dialysis. DIC, gut ischemia causing abdominal pain can also be the presenting features. The factors which precipitate CAPS are infections, surgical procedures, dental

Table 3: Treatment of APS related Bad Obstetrics History

Clinical Circumstance	Recommendation
>1 Fetal or >3 pre-embryonic losses, no thrombosis, APLA but no SLE	Prophylactic LMWH 0.5mg/kg/day + Low dose Aspirin 75mg/day throughout Pregnancy and 6-12 weeks postpartum
>1 Fetal or >3 pre-embryonic losses, no thrombosis, APLA with SLE	Prophylactic LMWH 0.5mg/kg/day + Low dose Aspirin 75mg/day throughout Pregnancy and 6-12 weeks postpartum+ Prednisolone + Hydroxychloroquine
Prior Thrombosis, regardless of pregnancy loss, APLA but no SLE	Therapeutic LMWH1.5mg/kg/day Or LMWH 1mg/kg/ twice a day + Low dose Aspirin 75mg/day throughout Pregnancy and 6-12 weeks postpartum; Warfarin after 12 weeks
Prior Thrombosis, regardless of pregnancy loss, APLA with SLE	Therapeutic LMWH1.5mg/kg/day Or LMWH 1mg/kg/ twice a day + Low dose Aspirin 75mg/day throughout Pregnancy and 6-12 weeks postpartum+ Prednisolone + Hydroxychloroquine Warfarin after 12 weeks
Only Antibody Positivity, no thrombosis, no SLE	Low dose Aspirin 75 mg/day throughout pregnancy

extraction, stoppage of anticoagulants or consumption of oral contraceptive pills. Sometimes pregnancy can be complicated by CAPS. The presence of CAPS during pregnancy can cause maternal as well as foetal mortality. The conditions which closely mimic CAPS are listed in Table 2.

LABORATORY INVESTIGATIONS

CBC shows thrombocytopenia, Direct Coomb's test may be positive. Detecting β_2 GPI dependant ACLA is the gold standard for ACLA. LAC should be checked by dilute Russell Viper venom time. The presence of one of the antibodies from ACLA, LAC or anti β_2 glycoprotein-I is enough to make the diagnosis. Multiple or triple positivity predicts the risk for recurrent disease. Histopathological evidence of multiple vessel occlusions in addition to APLA usually in high titres and clinical evidence of multiorgan failure is needed to diagnose CAPS. Thus kidney biopsy, skin biopsy, lung biopsy or biopsy of the small intestine may be needed in confirming the diagnosis of CAPS. The demonstration of any one of the antibodies 12 weeks apart is needed for the confirmation of the diagnosis of APS. However in resource limited settings due to

financial constraints, demonstration of the test only once may be sufficient to diagnose and treat the patient as a case of APS. Cases of secondary APS need other tests like ANA, thyroid function test, HIV, radiological tests like X rays, CT/MRI/USG in suspected cases of infection or malignancy.

TREATMENT

1. Patients who test positive only for the antibodies without any symptoms should be left alone. They do not need any treatment. There is no reported literature which supports prophylaxis with aspirin in primary prevention.
2. Patients with arterial or venous thrombosis need to be treated with heparin for acute thrombosis and warfarin to prevent the recurrence of thrombosis. It is necessary to maintain the INR between 2 to 3 for the patients who are on warfarin.
3. Since SLE is the most common rheumatological condition associated with secondary APS, the treatment of APS with and without SLE needs to be mentioned specially. Both the conditions, SLE and APS whether presenting in isolation or occurring together have a poor pregnancy outcome. Although with the increasing awareness about these conditions and its treatment options,

the pregnancy morbidity and mortality is changing to have a favourable pregnancy outcome. The treatment of recurrent pregnancy loss is depicted in Table 3.

4. Patients with APS who have thrombocytopenia, if platelet count is less than 50000, prednisolone and IVIG is recommended. If the platelet count is more than 50000, no treatment is needed.
5. CAPS needs to be treated aggressively with anticoagulation, steroids and IVIG or plasmapheresis.

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