CONTINUING MEDICAL EDUCATION

ANITPHOSPHOLIPID SYNDROME-CURRENT STATUS

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The antiphospholipid syndrome is an acquired multisystem disorder of hypercoagulation, which may be primary or secondary to underlying diseases. Serological markers include the lupus anticoagulant and anticardiolipin antibodies. Clinical features include recurrent thrombotic events, repeated foetal loss and thrombophlebitis, Cutaneous manifestations may occur as the first sign of antiphospholipid syndrome. These include livedo reticularis, necrotizing vasculitis, livedoid vasculitis, thrombophlebitis, cutaneous ulceration and necrosis, erythematous macules, purpura, ecchymoses, painful skin nodules, and subungual splinter haemorrhages. Antiphospholipid syndrome may also be associated rarely with anetoderma, discoid lupus erythematosus, cutaneous T-cell lymphoma, or disorders that closely resemble Sneddon syndrome. Non-inflammatory vascular thrombosis is the most frequent histopathologic feature observed. Prophylaxis and treatment of thromboses in patients with antiphospholipid syndrome relies principally on anticoagulant and antiplatelet agents.

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Antiphospholipid syndrome (APS), is a hypercoagulable condition that is associated with arterial and venous thrombosis, first identified in patients with systemic lupus erythematosus (SLE). APS is much more common than SLE and majority of the patients with this syndrome do not have SLE.[1] This condition is identified by the presence of antiphospholipid antibodies (eg. Anticardiolipin antibodies-ACL) a heterogeneous family of polyclonal immunoglobulins that bind with negatively charged or neutral phospholipid. When the syndrome is not associated with connective tissue diseases such as SLE, it is known as 'primary' APS (PAPS) and if it is associated with SLE, it is called as 'secondary' APS. PAPS is much more common than the secondary APS.[2]

Clinical Features

APS is suspected whenever arterial and venous thrombosis occur without predisposing factors. Other features of APS are thrombocytopenia, leg ulcers and recur-

rent foetal loss(3 or more) without any evidence of auto-immune disease.[3] The PAPS has a lower female to male ratio (2:1) in comparison to SLE(10:1).[4] The most common presentations of APS with regard to various systems are as follows:

(1) **Vascular system:** (a) Arterial thrombosis which is common in APS results in ischaemia and can virtually affect any organ in the human body and vessels of all sizes may be involved. In addition to stroke and transient ischaemic attack (TIA), the patient can present with myocardial infarction, blindness, Addison's disease (from adrenal thrombosis), hypertension (from glomerular thrombosis) with renal ischaemia and accelerated atheroma), pain in the limbs (limb ischaemia) and pain abdomen (bowel ischaemia). (b) Venous thrombosis results in deep vein thrombosis, hepatic vein thrombosis (BUDD - Chiari syndrome)and in fact any vein including thoracic outlet veins, inferior vena cava, retinal veins may be involved in APS.

(2) **Nervous system-** Neurological manifestations can occur as a result of small vessel thrombosis and the various clinical manifestations include stroke, TIA, sagital sinus thrombosis, headache (migraine), chorea, seizures, psychiatric disturbances, visual abnormality like amaurosis fugax, ischaemic optic atrophy, multi-infarct dementia and rarely transverse myelopathy, Guillain - Barre syndrome and inclusion body myositis.[5] Seventeen per cent of strokes occurring below 45 years of age are thought to be due to APS.[6] Snedden's syndrome may be one of the rare manifestations (triad of livedo reticularis, cerebrovascular occlusion and labile hypertension in the presence of aCL).[7]

(3) **Cardiovascular system** - Patients may present with acute mitral valve disease as a result of intracardiac thrombosis and mucinous degeneration of the mitral valve. APS may be confused with subacute bacterial endocarditis as some patients with this syndrome may have splinter haemorrhage and clubbing.[8] APS should be differentiated from rheumatic fever because of the presence of chorea and heart murmurs. Pulmonary hypertension is a recognised feature. It is believed that 20% of myocardial infarction in young patients may be due to APS.[4]

(4) **Reproductive system**- Twenty-seven percent of women who have history of more than two abortions probably suffer from APS.[6] Usually these patients have first trimester miscarriage or late foetal loss with evidence of intrauterine growth retardation. Pre-eclampsia has also been reported. Placental vessel thrombosis and the resultant ischemia seem to be responsible for most of these clinical features.

(5) **Renal system** - Bilateral renal vein thrombosis may occur . In patients suffering from a malignant hypertension with renal insufficiency without obvious SLE may be suspected to have APS.[4]

(6) **Haematological disorders-** Thrombocytopenia and haemolytic anaemia can occur.

(7) **Cutaneous manifestations-** livedo reticularis (lace-like pattern of cyanosis) in dorsum of hand and lower extremities in association with painful ulceration and purpuric spots or occasionally with frank gangrene of extremities can occur. Recurrent skin ulcers or necrotising purpura may also be present. Livedo reticularis is due to involvement of dermal vessels.

(8) **Miscellaneous-**APS may also be associated with Sjogren's syndrome, inflammatory polyarthritis, vasculitis and subacute cutaneous lupus.[4] Avascular necrosis of femoral head is a rare feature of APS.[4]

Widespread organ failure along with thrombocytopenia, adult respiratory distress syndrome and sudden collapse are serious manifestations of APS and is known as "catastrophic" APS.[8]

Mechanism of Thrombosis

The exact mechanism(s) involved in the pathogenesis of thrombotic events in APS are not clear. But the probable mechanisms suggested are as follows:

(1) The antibodies directed against phospholipids may act on endothelial and/or thrombocyte membrane and interfere with the release of prostacyclin or endothelial plasminogen activator.[8]

(2) The antibodies may affect clotting proteins (eg, thrombomodulin of protein C or protein S) present on the surface of cell membranes with the help of a cofactor called apolipoprotein H (B2-glycoprotein I).[3, 8]

(3) Inhibition of protein C activator (thus accelerating clotting process), inhibition of fibrinolysis or inhibition of antithrombin III activity may be responsible for thrombosis in APS.[3, 5]

Types of aCL Thrombosis Syndromes

Type I (commonest) - Deep venous thrombosis with or without pulmonary embolism.

Type II - Thrombosis affecting coronary artery, aorta or peripheral artery.

Type III - Retinal or cerebrovascular thrombosis.

Type IV- Admixture of type I, II and III.

Investigations

The five types of antiphospholipid antibodies are.[9]

(1) Lupus anticoagulants
(2) Anticardiolipin antibodies (aCL)
(3) Reaginic antibody
(4) Specific antibodies to anionic phospholipids
(5) Specific antibodies to neutral phospholipids.

Of all, the first type of antibodies have clinical significance.[3] APS encompasses both LA and aCL antibodies, and it is seen that the patient may have both the antibodies in approximately 60% cases and the remaining 40% have only one type of antibody.[9] LA was first described in SLE in which the prevalence of LA and aCL antibodies ranges between 10% and 50%; on the other hand, the prevalence of LA and aCL in the general population is about 3.6% and 4-6% respectively.[5,10]

Diagnosis of APS based on the Detection of Antibodies[3]

(A) Lupus anticoagulant- It is a misnomer because paradoxically it is associated with thrombosis rather than haemorrhage. The tests currently used to screen LA are : (i) Prolongation of activated partial thromboplastin time (aPTT) and prolongation kaolin clotting time (KCT). (ii) Demonstration that the abnormality in coagulation is due to the presence of an inhibitor to an individual clotting factor rather than to the deficiency of the factor(s) and the inhibitor is directed against phospholipids.

(B) Anticardiolipin antibodies

(C) Reaginic antibody - Persistently positive VDRL test.

The anticardiolipin antibodies are detected by solid-phase enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay (RIA).

Thus to diagnose APS, coagulation testing for reaginic antibody should be done.[9] IgG, IgM and I_gA ideotypes of aCL antibody can be detected by ALISA. Increased blood level of IgG aCL antibody is found in patients with recurrent abortions.[4] It should be remembered that aCL antibody is also found in idiopathic thrombocytopenic purpura, leukaemias, certain infections (mycoplasma, Gram-negative infections, hepatitis C, HIV ,malaria,), malignancy or drug therapy ([procainamide, valproic acid, amoxycillin, chlorpromazine, phenytoin).[3,4] Antinuclear factor (ANF) is usually negative and ESR is usually within normal limit.[6]

Diagnostic criteria for APS[11]

(A) Clinical features - (a) Recurrent venous or arterial thrombosis. (b) Recurrent foetal loss (c) Thrombocytopenia.

(B) Serological features -(a) IgG aCL>20 GPL ((IgG phospholipid);(b) LA: (c) LgM aCL >20 MPL (IgM phospholipid) plus LA.

One clinical feature and one serological feature should be present to diagnose APS. One GPL or MPL unit is equivalent to one micro g of affinity purified IgG or IgM ideotypes of aCL.[12]

Other investigations that can be done to derive further support in the diagnosis of APS may include:

(a) Haemogram : Total and differential blood count ; reticulocyte and platelet count, ESR (b) ANF. (c) Chest x-ray, ECG,

echocardiography (d) Liver function tests (e) CT scan of brain (f) Assessment of renal function ,etc.

APS should be suspected whenever the following features are present in the patient:

(1) Venous thrombo-embolism in patients below 45 years of age.

(2) Arterial thromboembolism presenting below 45 years of age in the absence of risk factors.

(3) Three or more abortions of unknown aetiology.

(4) Early, severe pre-eclampsia.

(5) In diseases like ischemic optic atrophy, chorea, livedo reticularis, Budd-Chiari syndrome, etc.

Treatment

No definite treatment strategy is yet suggested for APS. The antiphospholipid antibodies persist for years, possibly for a lifetime.[13] Different regimens suggested include low-dose aspirin, immunosuppressive drugs like corticosteroid, anticoagulation with warfarin heparin, and pasmapheresis.[3,6] Low-dose aspirin is an effective prophylaxis against both venous and arterial thrombosis, and patients with thrombosis (eg. stroke) associated with APS should receive long-term anticoagulation therapy, with or without low-dose aspirin.[14] Until further information becomes available, one approach is to offer low-dose aspirin to women with three or more episodes of foetal loss and a positive test for aCL antibody.[3] Intravenous high dose immunoglobulin or plasma exchange has been tried in patients with recurrent foetal loss. Some authors advocate low-dose subcutaneous heparin in venous thromboembolism for APS.[15] An ongoing prospective, randomised trial comparing aspirin with warfarin for the prevention of stroke will not be completed until 1997.[16]

In summary, Type I and II disease are usually treated by heparin whereas type III patients where cerebrovascular accidents occur, can be given long-term anticoagulants like low-dose aspirin (75 mg daily).[7] Type III patients with retinal vessel occlusion are treated by pentoxyphylline (400 mg four times daily).[4] Low dose aspirin definitely improves the pregnancy success rate.[3] Aspirin is used initially in the prophylaxis against recurrent miscarriages and prophylactic doses of heparin is tried where aspirin fails.

Conclusion

It is mandatory to do a blood level of aCL antibody and to search for livedo reticularis or any cardiac murmur whenever any young person presents with migraine, stroke or recurrent abortion. Detection of aCL antibody in patients with Budd-Chiari syndrome is now a standard practice as APS is thought to be the second most common cause of hepatic vein thrombosis.[8] It is said that APS is not as rare as it is believed.

In view of the fact that atherosclerosis occurs in an accelerated fashion in APS and there is cross-reactivity of aCL antibody with low density lipoprotein (LDL), it would rather be useful if immunological studies of atherosclerosis includes evaluation for APS.

References

1. Hughes GRV. Thrombosis, abortion, cerebral disease and lupus anticoagulant. BMJ 1983;287;1088-1089.

2. Anderson RA. A primary antiphospholipid syndrome? J Rheumatol 1988;15;1742-1746.

3. Pattison NS, Birdsall MA, Chameley LW, et al. Recurrent foetal loss and the antiphospholipid syndrome. In: Bonner J,editor. Recent Advances in Obstetrics and Gynaecology, NO.18 Edinburgh: Churchil Livingstone, 1994;23-50.

4. Ran UR. Anti-cardiolipin antibodies. In:Shankar PS, editor Medicine Update. Vol.5 1st ed, Bombay Association of Physicians of India 1994; 42:826-827.

6. Huskisson EC, Drury PL. Rheumatology and bon disease. In: Kumar P, Clark M.editors, Clinical Medicine-A Textbook for Medical Students and Doctors, 3rd ELBS ed 1994;403.

7 Dalai PM, Dalal KP. Antiphospholipid antibody syndrome In: Harris R. Mc Gregor A M, Doherty M, Deighhton C.editors. Medicine International No 3 Indian ed., Abingdon, UK: The Medicine Group (Journals) Ltd. 1994,65-66.

8. Hughes GRV. Antiphospholipid antibody syndrome In: Harris R.McGregor A.M. Doherty M, Deighton C.editors. Medicine International No.3 Indian ed., Abingdon, UK: The Medicine Group (Journals) Ltd. 1994; 65-66.

9. Triplett DA. Lupus anticoagulants. In: Poller L, editor, Recent Advances in Blood Coagulation, No 6, Edinburgh: Churchil Livingstone,1993;91-103.

10) Shi W. Krilis SA, Chong Bh, et al . Prevalence of lupus anticoagulant and anticardiolipin antibodies in a healthy population, Aust N Z J Med 1990; 20:231-236.

11) Harris EN. A reassessment of the antiphospholipid syndrome, J Rheumatol 1990;17;733-735.

12. Hughes GRV. The antiphospholipid syndrome:ten years on. Lancet 1993;342:3412-344.

13. Khamasta MA, Caudrado MJ, Mujic F, et al.The management of thrombosis in the antiphospholipid antibody syndrome, N Engl J Med 1995; 332:993-997.

14. Thromboembolic Risk Factors (THRIFT) Consensus Group-Risk of and prophylaxiz for venous thromboembolism in hospital patients. BMJ 1992;305;567-574.

15. BreyRL. Stroke prevention in patiets with antiphospholipid syndrome. Lupus 1994;3:299-302.