Introduction

Realms of copy have been written on the Anti Phospholipid Antibody (APLA) syndrome in the past two decades. Since this is a relatively new syndrome, new information regarding pathogenesis, clinical features, laboratory tests and therapy continues to flood us. In spite of this, several vexatious issues remain unanswered. In this article, we would attempt to address these issues in the light of the new insight obtained.

The description of the anticardiolipin syndrome as Graham Hughes then called it in 1983 was a wonderful example of astute clinical observation complemented by laboratory research. Although APLA was first described in the context of lupus, the syndrome has now become the domain of every subspeciality in the field of medicine. Population studies identify APLA as one of the commonest causes of thrombophilia, accounting for 20% of cases of recurrent thrombosis among young patients.

What Constitutes APLA Syndrome?

Definition

The occurrence of recurrent venous and/or arterial thrombosis or pregnancy losses in the presence of high levels of anticardiolipin antibodies or positivity on lupus anticoagulant test constitutes the antiphospholipid syndrome as originally defined.

However more recent work has revealed that patients with APLA can have antibodies directed against other phospholipids. These include phosphatidyl inositol, phophatidyl serine, phosphatic acid, prothrombin and B2GPI; the phospholipid binding plasma protein. Antibodies directed against B2 glycoprotein 1 in particular seems to be very important in the pathogenesis of the syndrome.

Pathogenesis of APLA

Better understanding of the pathogenesis of APLA provides potential opportunities to interrupt the processes leading to thrombosis at various levels. APLA most likely plays a primary pathogenetic role; inducing proadhesive, proinflammatory and procoagulant molecules. APLA directed against B2 glycoprotein bind to vascular endothelial cells leading to increased expression of adhesion molecules...
and leukocyte adherence to the endothelium. This endothelial activation leads to increased expression of tissue factor and production of cytokines. Tissue factor is the physiologic initiator of normal coagulation and is not normally expressed on cells in contact with flowing blood. In addition to the above, direct inhibition of activated protein C pathway and abnormalities in platelet function are other suggested mechanisms to explain the prothrombotic activity of APLA.

Role of HMG CoA Reductase
HMG CoA reductase catalyses the synthesis of Mevalonate from the substrate HMG CoA. Mevalonate serves as a substrate for the synthesis of cholesterol. It is also a precursor of isoprenoid intermediates necessary for prenylation of important intra cellular signalling molecules including Rho, Ras and Rac. (Fig. 1)

Inhibition of this signaling leads to increased nitric oxide synthase activity in endothelial cells and platelets, decreases platelet activation, increases endothelial cell fibrinolytic activity and decreases expression of endothelin I. Such inhibition (by drugs like Statins) would be expected to have salutory effects in a condition like APLA.

Clinical Features of APLA
Repeated pregnancy losses, recurrent arterial and venous thrombosis, thrombocytopenia and livedo reticularis are readily recognised features of APLA syndrome.

However with increasing awareness, a myriad of conditions are being recognised as possibly caused by APLA. Epilepsy, migrane, cognitive dysfunction, a multiple sclerosis like condition, cardiac valve vegetations, malignant hypertension with renal insufficiency, auto-immune hemolytic anaemia are some such conditions where a high index of suspicion is needed to make the diagnosis.

Such patients may not fulfil the usual criteria for the diagnosis of the syndrome adding to the complexity.

The catastrophic antiphospholipid antibody syndrome (CAPS) is characterized by extensive thrombosis affecting the vasculature of multiple organs like the heart, liver, kidneys, intestines and lungs. It is associated with upto 50% mortality.
Factors Triggering or Aggravating the Procoagulant State
It is well known that not all patients with APLA have a thrombotic episode. Traditional risk factors like hypertension and smoking were found to increase the risk of arterial thrombosis in one study. Pregnancy and surgical procedures also increased the risk. In this study, use of hydroxychloroquine and or aspirin was thought to be protective for asymptomatic APLA patients. The concomitant presence of two or more prothrombotic factors including the presence of factor V Leiden, prothrombin mutation, deficiency of protein C, protein S and antithrombin III or hyperhomocysteinaemia probably enhances the risk of thrombosis.

In a relatively large series of patients with catastrophic antiphospholipid antibody syndrome, infections, oral contraceptives, pregnancy and drugs were identified as possible triggers.

Laboratory Criteria for the Diagnosis of APLA Syndrome
a. Anticardiolipin antibody
   1. IgG or IgM isotype present in medium or high titre six weeks or more apart.
   2. B2Gycoprotein I dependent anticardiolipin antibody
b. Lupus anticoagulant
   Demonstration of a prolonged phospholipid dependant coagulation test. e.g. APTT, Kaolin clotting time, Russel Viper Venom time, dilute prothrombin time.
   The presence of any one laboratory criteria with atleast one clinical criterion (vascular thrombosis / pregnancy morbidity) is necessary to make the diagnosis.
   It is necessary to screen patients for both tests (a & b) as these are not synonymous. 80% of patients with lupus anticoagulant may have ACLA however, only 20% patients with ACLA will be positive for lupus anticoagulant. These tests possess a high sensitivity but low specificity.

After the introduction of assays for B2GPI and other phospholipid antibodies, it was thought that the diagnostic yield of APLA positivity would improve considerably. However this is expensive and additional yield is negligible. For all routine purposes, therefore use of ELISA anticardiolipin antibody and the lupus anti coagulant test is considered adequate.

It is important to recognize that there is a class of patients with typical diagnostic features of APLA who consistently test negative for a battery of laboratory tests for anticardiolipin antibodies. It has been suggested that this entity should be called sero negative APLA, similar to seronegative RA or sero negative lupus.

Treatment of APLA Syndrome
We shall look at the present day accepted therapies first, then newer therapies in the offing and lastly move to contentious issue in treatment.

It is now accepted universally that steroids have no role in the management of APLA except perhaps in the catastrophic APLA syndrome. The main stay of treatment for APLA with thrombosis presently is therefore anti coagulation ± anti platelet therapy.

Treatment of patients with a thrombotic episode:
1. The point where there is reasonable consensus is the treatment of a patient who has had an arterial / venous thrombosis with high titre APLA positivity. This calls for oral anticoagulation, presently accepted to be life long and with the aim of maintaining the INR between 3.1 – 4.0.
   Interestingly, in a recent study, a total of 114 patients with prior thrombosis (APLA) were treated with either moderate intensitiy warfarin (INR between 2.1 – 3.0) or high intensity Warfarin with a follow up period of 2- 7 years. Only patients with moderate or high titres of anti cardiolipin antibodies or lupus anticoagulant were included in the study.
   The results : The risk of thrombosis was low and comparable in both the groups.
Despite some of its limitations, the study makes a strong case for use of less intensive anticoagulant therapy in patients with APLA and thrombosis. This is particularly heartening in the Indian context, where putting a patient on high dose warfarin is often a hazardous proposition.

2. Pregnancy with prior fetal losses:
   In pregnancy and APLA with prior fetal losses ± thrombosis, different permutations of therapy have been tried. Low dose aspirin alone, low dose aspirin and heparin, heparin alone, heparin in the first trimester followed by warfarin in the second and third trimester have all been tried. While few studies suggest that heparin use with aspirin improves outcome, a more recent study found aspirin alone to be as effective as aspirin and heparin. Treatment should continue through the pregnancy up to 6 weeks post partum.
   In pregnant women with prior thrombosis, high dose subcutaneous heparin (> 10,000 units twice a day) or low molecular weight heparin is recommended on the basis of present data.\textsuperscript{14, 15} Low molecular wt. Heparin is preferred due to its convenience, low risk of heparin induced thrombocytopenia and osteoporosis and the improved antithrombotic to anticoagulant ratio.\textsuperscript{16}

Treatment of the Catastrophic Antiphospholipid Antibody Syndrome:\textsuperscript{8}
Survival from this syndrome is only 50% and the number of patients are relatively less. Justifiably therefore there is a lot of empiricism in treatment. Corticosteroids, intravenous immunoglobulin and plasmapheresis have been used in various combinations in addition to anticoagulation with improvement in survival in reported cases.

Newer Therapeutic Options
These options are based on the pathogenetic mechanisms of anti phospholipid antibodies discussed earlier in this article.

1. Hydroxy chloroquine: The use of hydroxychloroquine has been associated with a decreased risk of thrombosis in SLE patients with APLA.\textsuperscript{17} In animal models, hydroxychloroquine has been shown to decrease thrombus size and inhibit platelet activation induced by APLA. It may also be useful due to its immune modulatory effects.

2. Statins: As discussed earlier, interruption of the conversion of HMG CoA reductase to mevalonate can have pleiotrophic effects. In an animal model, uvastatin, significantly diminished APLA mediated thrombosis and endothelial cell activation in vivo.\textsuperscript{18} Statins therefore may prove to be very useful drugs in the prevention of thrombosis, although there is not enough literature on the subject in humans today.

3. ACE inhibitors: These, like statins inhibit expression of tissue factor on monocytes.

4. Dilazep: An adenosine uptake inhibitor and anti platelet agent similar to dipyridamole.

5. New oral anti coagulants: Ximelagatran, an inhibitor of thrombin is being developed for clinical use. Its advantage over warfarin is that it has a fixed dose schedule and does not require coagulation monitoring.\textsuperscript{19}

Contentious Issues\textsuperscript{19, 22}
There are several contentious issues in treatment

1. Treatment of the asymptomatic patient who is APLA positive / APLA +ve pregnant patient with no pregnancy losses.

2. Treatment of the patient who does not respond to standard anticoagulation.

3. Do all patients with APLA warrant life long treatment?

Does long period of absence of thrombotic episodes with conversion to APLA negativity warrant scaling down / stopping treatment? In the context of secondary APLA particularly, where thrombosis could be multifactorial and APLA may be part of a non specific immune activation can one consider stopping anticoagulation if APLA is negative at a later date.
1. Treatment of asymptomatic APLA positive person:
The answer to this presently is that no treatment is required. Interestingly, a retrospective study in women in whom antiphospholipid antibody was diagnosed during pregnancy has suggested that treatment with low dose aspirin provides protection against thrombosis. Some prospective trials which are under way, will provide definite answers to this question.

2. Long term continuation of anticoagulation:
There is no doubt that in patients with APLA, there is a high chance of recurrence of thrombosis and therefore the need for continued anticoagulation. However, certain patients with APLA experience thrombosis in the setting of other non recurrent trigger factors (e.g. oral contraceptive, nephrotic syndromes etc.) Other patients revert to APLA negativity after initial diagnosis. In these situations, it may perhaps be possible to reduce the level of anticoagulation, convert the patients to aspirin or use safer therapy like statins or hydroxychloroquine.

The answer to these questions is presently unclear but prospective long-term trials in patients without prior thrombosis hold the promise of providing some of the answers.

References
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