Review Article

The antiphospholipid syndrome

RAHUL GROVER, ASHOK KUMAR

ABSTRACT

The antiphospholipid syndrome encompasses a wide spectrum of presentations cutting across all subspecialties of medicine. It is characterized by recurrent thrombotic events involving both the arterial and venous systems. Large arteries and veins as well as the microcirculation are involved. Recurrent strokes, myocardial infarction, pulmonary embolism, gangrene of the digits, etc. cause much morbidity and mortality in affected patients. It is recognized as an important cause of recurrent pregnancy loss. The risk in pregnancy extends to a propensity towards pre–eclampsia, abruptio placentae and intrauterine growth retardation. It often manifests as asymptomatic thrombocytopenia and sometimes as a life–threatening form called catastrophic antiphospholipid syndrome. The management of thrombotic events rests on high grade anticoagulation (INR 3–4) as lower values of INR than this often fail to prevent recurrence. Aspirin is generally added in case of arterial thrombosis. A combination of heparin and aspirin at least in the first trimester and sometimes throughout pregnancy is used to prevent foetal loss.

Natl Med J India 2003;16:311–16

INTRODUCTION

The antiphospholipid syndrome (APLS) or the Hughes syndrome is now a well recognized autoimmune disorder characterized by a procoagulant state and presence of antiphospholipid antibodies (aPL) in the blood. It leads to a wide spectrum of clinical manifestations of varying severity which encompass many clinical disciplines. Two laboratory findings in patients suffering from systemic lupus erythematosus (SLE) led to the recognition of APLS. The first was prolonged whole blood clotting time and prothrombin time in 8 patients with no bleeding tendency reported by Conley and Hartmann in 1952.[1] None of the patients had any clotting factor deficiency. Later, the term lupus anticoagulant (LAC) was assigned to this phenomenon. Bowie *et al*. reported its association with a paradoxical increased propensity for thrombosis in 1963.[2] The second laboratory abnormality was the presence of a false-positive test for syphilis. This was due to a complement-fixing antibody directed against cardiolipin. In 1983, Harris *et al*. developed a solid phase immunoassay for cardiolipin (a type of phospholipid) that was several hundred times more sensitive than the VDRL test, and documented a positive correlation between anticardiolipin antibodies (aCL) and the LAC phenomenon, thrombotic episodes, recurrent pregnancy losses and thrombocytopenia.[3] Love and Santoro confirmed the association in a meta-analysis in 1990; a significantly larger proportion of patients with SLE having LAC or aCL suffered from thrombotic complications than those without LAC or aCL.[4] Asherson *et al*. reported 70 patients with APLS without underlying SLE or any related disorder.[5] Thus came the concept of primary antiphospholipid syndrome (PAPS). It is now recognized to be more common than secondary APLS and, in 1998, a meta-analysis was published characterizing PAPS.[6]

Several workers from India have published their experience of APLS.[7–12] However, cases seem to be under-reported.

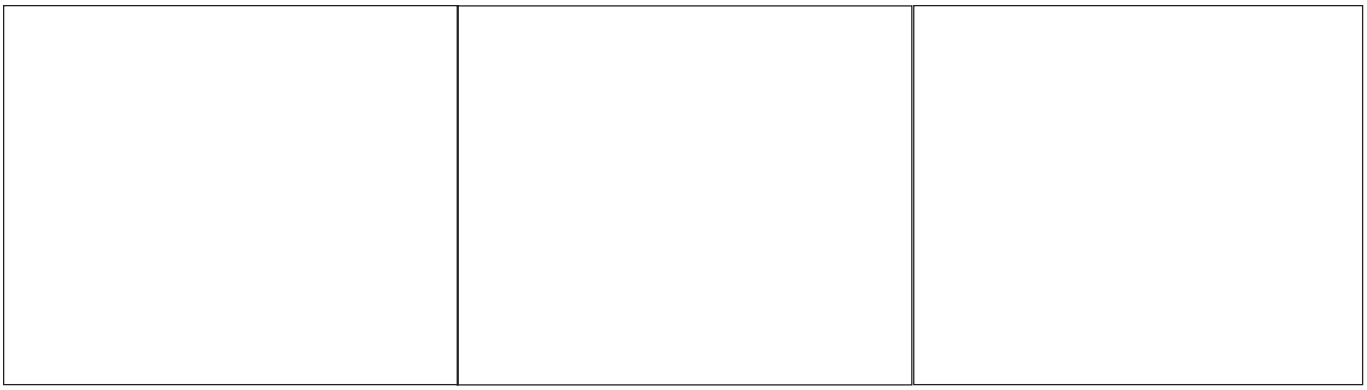
PATHOGENESIS

Antiphospholipid antibodies (aPL) are believed to be responsible for the clinical manifestations of APLS. Broadly, aPL can be divided into two types: those specific for cardiolipin, i.e. aCL; and those responsible for the LAC phenomenon. A substantial overlap of the two is observed in patients.

Contrary to the earlier belief, the targets for these antibodies are not phospholipids but phospholipid-binding plasma proteins. A number of proteins are recognized as the target antigens, the most important being b2GP1 and prothrombin. The exact mechanism by which these antibodies lead to thrombotic and other complications is not well understood. The current concept is that these antibodies interact with coagulation factors at the phospholipid membrane, which shifts the delicate balance to a procoagulant state *in vivo* and anticoagulant state *in vitro*.[13] aPL forms a bivalent antigen–antibody complex. This has an increased affinity for phospholipids and competes with annexin V (a molecule that coats the cell surface and has anticoagulant properties) for the catalytic surface on the cell membranes.[14] Also, the binding of aPL to membrane phospholipids alters the protein C pathway, interferes with its activation, and thus induces a procoagulant state. The binding of aPL to endothelial cells transforms them to a proadhesive (increased expression of adhesion molecules such as intercellular adhesion molecule [ICAM], vascular cell adhesion molecule [VCAM], etc.), procoagulant (increased tissue factor expression) and proinflammatory (release proinflammatory cytokines) phenotype (Fig. 1).[15] While the phospholipid surface used in *in vitro* assays favours an anticoagulant effect, the microenvironment *in vivo* favours a procoagulant effect. Other mechanisms such as oxidant-mediated injury, damage to cell membranes with exposure of anionic phospholipids have also been proposed to play a role in the pathogenesis.[16–18]

Not all aPL are pathogenic. Occasionally, they can be positive in infections (HIV, EBV), drug therapy (procainamide, phenothiazines, oral contraceptives), malignancies, vasculitis and even in normal people.[19–21] They differ in the IgG subclass and often

All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India
RAHUL GROVER, ASHOK KUMAR Clinical Immunology and Rheumatology Service, Department of Medicine
Correspondence to ASHOK KUMAR; *ashok_145@hotmail.com*



A. Competitive displacement of Annexin V on the phospholipid membrance by aPL

B. Inhibition of protein C pathway by aPL

C. Endothelial activation by aPL causing 'procoagulant milieu'

FIG 1. Diagrammatic presentation of current hypothesis on the causation of a prothrombotic state by antiphospholipid (aPL) antibodies (modified from reference 15)

occur in low titres although the distinctions are not always clear. Moderate to high titres of aPL that persist for more than 6 weeks help in distinguishing pathogenic from non-pathogenic aPL.

SPECTRUM OF APLS

Vascular thrombosis, obstetric complications and thrombocytopenia are recognized as the classical manifestations of APLS. Both arterial and venous thromboses occur in this syndrome, a feature not seen in other conditions associated with thrombophilia. Also, the thromboses tend to recur in the same territory. A wide spectrum of clinical manifestations of APLS are now recognized and can involve any organ. A range of neurological presentations is recognized, varying from headache to syndromes mimicking multiple sclerosis. The clinical manifestations according to the organ system involved are given in Table I. A severe, acute, life-threatening form associated with thrombosis in multiple organ systems is also recognized and is called catastrophic APLS. A high index of suspicion is necessary to recognize these conditions.

A recent multicentric study documented the clinical and immunological features and manifestations in a large cohort of 1000 patients with definite APLS.[22] This study showed that the majority of patients were women (82%). Most of the patients were adults with 3% having an onset of APLS in childhood. PAPS constituted the majority of cases (53%). SLE-associated APLS (36.2%) was the second leading cause. Thrombotic manifestations, particularly deep vein thrombosis (32%), thrombocytopenia and livedo reticularis were very common at the initial presentation. Foetal loss had occurred in 8.3% at presentation. All the systems were affected; neurological manifestations occurred in 20% of patients. Catastrophic APLS occurred in <1% of patients. Chorea and jugular vein thromboses were more common in childhood. Seventy-two per cent of the women in this cohort had had one or more pregnancies and 74% had succeeded in having a live birth while on treatment. Early foetal loss (<10 weeks) occurred in about one-third (35.4%), and 48% of pregnancies (out of 1580) had a successful outcome with 10% being preterm deliveries.

TABLE I. Spectrum of the antiphospholipid syndrome

Foetal	Early foetal loss, late foetal loss, premature birth, intrauterine growth retardation, stillbirth, neonatal death
Obstetric	Pre-eclampsia, eclampsia, abruptio placentae
Peripheral thrombosis	Deep venous thrombosis in upper and lower limbs, superficial thrombophlebitis, arterial thrombosis of legs, subclavian and jugular vein thromboses
Neurological	Stroke, transient ischaemic attacks, multi-infarct dementia, epilepsy, cerebral venous thrombosis, psychiatric symptoms, chorea, acute ischaemia of the eyes (retinal and choroidal vessels), sensorineural deafness, migraine
Cutaneous	Livedo reticularis, cutaneous ulcers, pseudovasculitis, gangrene, skin necrosis, nodules, splinter haemorrhages
Haematological	Thrombocytopenia, haemolytic anaemia
Cardiac	Valve disease, myocardial infarction, angina, cardiomyopathy, vegetations and intracardiac thrombus
Pulmonary	Pulmonary embolism, pulmonary arterial hypertension, pulmonary microthrombosis, pulmonary haemorrhage
Abdominal	Renal and mesenteric ischaemia, splenic infarct, Addison disease, pancreatitis, Budd–Chiari syndrome

DIAGNOSIS

Patients with APLS have a varied clinical presentation and are thus seen by different specialists. In various studies different cut-off titres for aCL were used, and a spectrum of symptoms was described, making it difficult to assess the importance of each association. To make useful comparisons, a preliminary set of criteria for the diagnosis of definite APLS was reached in 1999[23] (Table II). The criteria encompassed the clinical and laboratory

TABLE II. Consensus Classification Criteria, 1999 for definite antiphospholipid syndrome[23]

Clinical criteria

A. *Vascular thrombosis*: One or more episodes of arterial, venous or small-vessel thrombosis, occurring within any tissue or organ.

B. *Complications of pregnancy*: One or more unexplained deaths of morphologically normal foetuses at ³10 weeks of gestation,
or
One or more premature births of morphologically normal neonates at <34 weeks of gestation,
or
Three or more unexplained consecutive spontaneous abortions at <10 weeks of gestation.

Laboratory criteria

A. *Anticardiolipin antibodies*: Anticardiolipin IgG or IgM antibodies present in moderate or high titres on 2 or more occasions at least 6 weeks apart,

B. *Lupus anticoagulant phenomenon*: Lupus anticoagulant antibodies detected on 2 or more occasions at least 6 weeks apart.

Note: A diagnosis of APLS requires one clinical and one laboratory criterion

features that were most closely associated with APLS in prospective studies and were based on strong experimental evidence. Possible and probable APLS were, however, not defined.

Evidence for aPL can be obtained either with a positive result of aCL or LAC. Both the tests are recommended and either or both may be positive in a given case. The risk for thrombotic complications is more in patients having LAC than those with aCL (6 times *v.* 2 times).[24] It is important to demonstrate the positivity of aPL on two occasions, at least 6 weeks apart. For aCL the titres should be moderate to high (the cut-off levels will vary with the population: 15–20 units are considered low, 20–40 units moderate, and above that high titres). aCL is generally of the IgG class but some patients may have only the IgM class of aCL. In a recent meta-analysis, 87.9% of the patients had either of these in a significant titre, IgG alone in 43.6% and IgM alone in 12.2%.[22] LAC is performed by a 3-phase test. In the first step, prolongation of coagulation is documented in at least one phospholipid-dependent assay (e.g. dilute prothrombin time for extrinsic pathway, dilute activated partial thromboplastin time (APTT) or kaolin clotting time for internal pathway, and Russel viper venom time for the common pathway). The second step is the failure to correct the above by adding normal plasma and the third is reduction or improvement in the above by adding excessive phospholipids.

TREATMENT

Thrombosis (Table III)

About 50% of patients at the onset have arterial and/or venous thrombosis with the cumulative figure rising with time. Patients with APLS who develop an initial episode of thrombosis are at an increased risk for recurrent thrombotic events. Management involves a standard approach to treat acute vascular thrombosis.[25] However, there are some issues requiring special attention: intensity and duration of anticoagulation, monitoring of anticoagulants, and whether or not to combine aspirin with anticoagulants.

Duration of therapy

The usual standard of care for patients (other than APLS) who have had 1 episode of venous thrombosis or pulmonary embolism is 6 months of anticoagulant therapy.[26] This is, however, not adequate for patients with APLS. In a study in which patients were randomized to indefinite anticoagulation versus 6 months of anticoagulant therapy, the relative risk for recurrence of thrombosis was 8 times more in the 6-month group. Although the risk for haemorrhage was much less (0.3), it did not translate into any difference in mortality.[27] Similar results have been highlighted in retrospective studies.[28–30] Derksen *et al*. found that 100% of patients on anticoagulants were free of recurrence at 8 years compared to only 22% who had discontinued anticoagulants.[28] Although the ideal duration has not been defined, a short course seems to be inadequate. Perhaps such patients should be on lifelong treatment.

TABLE III. Management options in antiphospholipid syndrome (APLS)

Clinical manifestation	Recommended treatment
Arterial thrombosis (chronic)	High grade (INR 3–4) anticoagulation, antiplatelet agents
Venous thrombosis (chronic)	High grade (INR 3–4) anticoagulation
Catastrophic APLS	Anticoagulation with heparin, plasmapheresis, steroids
Thrombocytopenia	Steroids, if symptomatic or counts <50 000/cmm; intravenous immunoglobulin, cyclosporin, chloroquine, dapsone and danazol in refractory cases
Avascular necrosis	No specific recommendations
Acquired hypoprothrombinaemia	Steroids

Note: Treatment of acute thrombosis is along standard lines. Anticoagulation is generally continued lifelong in established APLS.

Intensity of anticoagulation

Patients with APLS have been treated with various regimens providing high or low grade anticoagulant effect with or without added aspirin. Retrospective analysis and a recent decision analysis suggest that treatment with low grade anticoagulation (INR 1.5–2) or for short periods (3–6 months) is not very effective while long term, high grade anticoagulation (INR 3–4) is most effective.[29–31] Patients receiving anticoagulant therapy are at risk for bleeding complications (1%–5% per year) and have to make lifestyle adjustments during therapy.[32–33] In a recent study, a recurrence rate of 9.1 per 100 patient-years was found in patients with definite APLS on a regimen of high grade anticoagulation; thus, even high grade anticoagulation may fail.[34] The thrombotic episodes often recurred in the same territory. This regimen was also associated with a rate of major bleeds of 6 per 100 patient-years.[34] When thrombotic events continue to occur despite anticoagulation, low dose aspirin is often added in the case of arterial thrombosis. Very high anticoagulation (INR ~4.5) has also been tried occasionally. The picture is less clear for venous thrombosis because it causes relatively less morbidity; the benefits of the addition of aspirin are questionable and the risk of haemorrhage is definitely increased. The addition of aspirin increases the risk of bleeding complications by a factor of 1.25 without any major advantage.[31] A regimen of high grade anticoagulation followed by low grade anticoagulation has been suggested for paediatric patients. This is based on the lower perceived risk of recurrence in children due to lack of other risk factors such as atherosclerosis. This may help in reducing the frequency of bleeding.[32]

Monitoring during therapy

INR remains the gold standard for monitoring therapy with oral anticoagulants. Monitoring becomes a challenge when the patients are on heparin. The presence of LAC interferes with monitoring by APTT during heparin therapy. These patients can be monitored by chromogenic assays for individual vitamin K-dependent factors (factor Xa or protein C).

Acute venous thrombosis

The main goal of treatment is to prevent pulmonary thromboembolism. The standard measures include bed rest, elevation of the affected limb to allow oedema and tenderness to subside, and anticoagulant therapy. Heparin and warfarin should be started simultaneously to provide an overlap of about 5 days. Thrombolytics such as streptokinase, urokinase and tissue plasminogen activator (tPA) can be used but are not more effective in preventing pulmonary embolism. Thrombendarterectomy and percutaneous insertion of an inferior vena cava filter may be considered in special situations.

Acute arterial thrombosis

In a patient with APLS this usually means a transient ischaemic attack or stroke, with myocardial infarction and digital gangrene being less common. In some patients with acute stroke (<3 hours' duration), thrombolytics can be used but the standard of care is usually heparin followed by warfarin. Low dose aspirin is added

in patients who have repeated thrombotic events despite adequate anticoagulation. Clopidogrel and ticlopidine can also be considered. Very high grade anticoagulation (INR ~4.5) has also been tried in these patients. APLS patients with myocardial infarction can be treated with thrombolytics, angioplasty or coronary stenting. Peripheral arterial thrombosis can be treated with thrombolytics or heparin or angioplasty.

In both arterial and venous thromboses other associated conditions/risk factors (protein C or S deficiency in venous thrombosis, hyperhomocysteinaemia in arterial and venous thrombosis) must also be looked for and managed accordingly.[33]

CATASTROPHIC APLS

APLS with rapidly recurring thrombotic events involving multiple organs over a short period of time is termed catastrophic APLS (CAPS).[35–37] The brunt of the disease is borne by the small vessels and mortality exceeds 50% despite therapy. Both primary and secondary APLS can get complicated by CAPS. A triggering factor is identified in the majority such as infections, trauma (often minor), invasive procedures (e.g. endoscopic retrograde cholangiopancreaticography), tumours and withdrawal of anticoagulants. The disease presents itself with acute onset multiple organ failure. Pulmonary manifestations include acute respiratory distress syndrome (ARDS) and diffuse pulmonary haemorrhage; neurological deficits include delirium, seizures, status epilepticus, hemiparesis, etc. and renal complications include acute renal failure and hypertension (often malignant with papilloedema and haemorrhages in the fundus). Other features include splenic, portal and mesenteric vein thrombosis, adrenal insufficiency secondary to infarcts and haemorrhages, bone marrow infarction, livedo reticularis and cutaneous ulceration. Laboratory investigations reveal a picture of disseminated intravascular coagulation, thrombocytopenia, microangiopathic haemolytic anaemia, leucocytosis and a high erythrocyte sedimentation rate. aCL antibodies, especially of the IgG type, are present in high titres.[36,37]

Cardiovascular insults are the leading cause of mortality along with ARDS and diffuse pulmonary haemorrhage. In one study, recovery occurred in 62% of episodes treated with anticoagulants versus 23% of those not treated with anticoagulants. Steroids are also administered to limit the possibility of widespread vasculitis in patients with SLE. Plasmapheresis (as for thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome) is another therapeutic option.[37]

PREGNANCY AND APLS

APLS complicates pregnancy throughout its course. Foetal loss occurs both in the first and second trimesters. In addition, during late pregnancy there is an increased risk of abruptio placentae, intrauterine growth retardation and preterm delivery. Also, pregnancy being a hypercoagulable state on its own, the risk of thrombotic events is further increased during the antenatal period as well as the puerperium.

The exact risk of the various complications is still not established due to a lack of large prospective trials, especially for some associations such as abruptio placentae, intrauterine growth retardation, etc. The heterogeneity of the definitions used for the inclusion of patients in studies (number of pregnancy losses or the titre of aCL) further complicates the interpretation of data. This is highlighted by the fact that in a recent systematic review of therapeutic trials in patients with recurrent pregnancy losses in APLS, the authors found only 10 of the 575 trials suitable. Even among these trials the cut-off values for aPL were too low in a few; these would be excluded by the current criteria for definite APLS.[38] Consequently, the current therapy guidelines reflect expert opinions rather than scientific evidence.

Management of patients with recurrent pregnancy loss

Antiphospholipid antibody is a risk factor for pregnancy loss, both in patients with SLE (60% *v*. 13%) and in healthy nulliparous women (16% *v*. 7%).[4,39] The risk of pregnancy loss has been assessed in both low risk (women attending for routine antenatal visits) and high risk groups (those with a history of prior pregnancy losses). Among patients with low risk, aPL is found in 2.7%–7%, and they increase the risk of pregnancy loss by around 3 times (16%–25% *v*. 6%–10%).[39–41] There is one study on women in the high risk group (median losses 4, range 3–11) in whom 90% of the pregnancies associated with aPL ended as failures compared to 34% in those without aPL.[42] It is, therefore, evident that aPL increases the risk of pregnancy loss much more among patients with history of previous losses than those with no such history (90% *v*. 25%). The current diagnostic criteria for APLS include only patients with previous pregnancy losses. This high risk group definitely merits treatment. The role of therapy in the low risk group remains to be defined.

Multiple agents have been used for the treatment of pregnant patients with APLS (Table IV). Steroids were used with the purpose of suppressing aPL. One of the first successful outcomes was reported by Lubbe *et al*. in 1983.[43] Five out of 6 women with aPL treated with steroids (prednisolone 40–60 mg/day) and low dose aspirin delivered successfully. Four of these patients had SLE. The use of steroids is associated with side-effects such as sepsis, diabetes, hypertension, osteoporosis, premature delivery, premature rupture of membranes and eclampsia. Steroids were later shown to be ineffective and often detrimental to foetal outcome in prospective studies[38,44–46] and are no longer used as first-line agents for the management of APLS.

Aspirin has been widely used alone as well as in combination with heparin.[47] Its use was prompted by the consideration that inhibition of thromboxaneA2 synthesis with resultant vasodilatation as well as the antiplatelet effect will prevent thrombosis in the placenta and elsewhere. The evidence for some effect of aspirin alone came from non-randomized trials.[48,49] A recent randomized trial failed to show any benefit of aspirin alone over placebo.[50]

A trial by Cowchock *et al*. in 1992 found that heparin in combination with low dose aspirin was as effective as the combination of steroids with aspirin, without as many side-effects.[44] Since then this combination has been used extensively. Two trials found that patients with APLS receiving the combination did better than those receiving aspirin alone (80% *v*. 44% and 71% *v*.

TABLE IV. Management options in pregnancy with antiphospholipid syndrome

Recurrent pregnancy losses without previous history of thrombosis	Low dose aspirin (75–150 mg) throughout, heparin for at least the first 14 weeks (either low molecular weight heparin: enoxaparin 40 mg/day or dalteparin 5000 U/day, or unfractionated heparin 10 000 IU b.d.)
Recurrent pregnancy losses with previous history of thrombosis	Anticoagulation throughout pregnancy; start with heparin as above and switch to warfarin after 16 weeks of gestation
Management during labour and the puerperium in patients on long term anticoagulation	Switch to heparin until 1 week postpartum when warfarin can be resumed

42%).[51,52] It was found that 90% of the miscarriages occurred in the first trimester and the benefit of additional heparin was limited to this period. A recent large study cast doubts on the role of heparin during pregnancy.[53] It found that 72% and 78% of the 98 women randomized to the two arms delivered successfully, which was not statistically different.

Low dose aspirin should be started as early as possible and continued till delivery. There is controversy whether aspirin should be combined with low dose heparin (5000 units subcutaneously twice a day) in women with a bad obstetric history without any thrombotic events in the past. The duration of heparin therapy is also debatable. It is advisable that patients with a history of first trimester pregnancy losses may be treated till 20 weeks while those with later losses may be continued on heparin throughout. This approach needs to be checked in prospective controlled trials. It is advisable to give warfarin/low molecular weight heparin (LMWH) for 6 weeks during the puerperium to prevent venous thrombosis.

Intravenous immunoglobulin (IVIG) has been used successfully in some cases. A recent trial showed no benefit of IVIG over the aspirin–heparin combination.[54,55]

Management of pregnant patients with previous history of thrombosis

Patients with a previous history of thrombosis need to be continued on anticoagulants. These women are usually on warfarin. This should be discontinued within 2 weeks of conception to avoid its teratogenic effects. Heparin (LMWH or unfractionated) is used to provide anticoagulation. LMWH may cause less osteoporosis, has a longer half-life and is equally effective; 10 000 units b.d. of unfractioned heparin, 40 mg o.d. of enoxaparin or 5000 units o.d. of dalteparin are commonly used. Therapy is continued during labour and the patient is switched to warfarin 1 week into the postpartum period.

THROMBOCYTOPENIA

Thrombocytopenia has been one of the three classical features of APLS. It is known to occur in 30% of patients suffering from APLS.[56] However, it is not included under the category of definite APLS. In the majority, it is mild and does not require any treatment. The pathogenesis of thrombocytopenia in APLS is still debated. There is evidence that antibodies directed against glycoproteins on the platelet surface rather than aPL are responsible. These are the same antibodies that are found in patients with idiopathic thrombocytopenic purpura (ITP).[57–59] Also, in a series of patients with chronic ITP, aPL was found in up to 30% of patients. Treatment is contemplated when the platelet count drops to <50 000/cmm and is on the lines of ITP. Corticosteroids are the mainstay while other agents such as IVIG, cyclosporin, chloroquine, dapsone and danazol have been used. Splenectomy has a limited role only, and is often ineffective. The occurrence of thrombosis in patients with thrombocytopenia poses a tricky problem. Such patients are treated with steroids and anticoagulants are added once the platelet count is ³50 000/cmm.

MISCELLANEOUS

Acquired hypoprothrombinaemia

This is a rare complication of APLS. It is believed to be due to high affinity antiprothrombin antibodies. Rapid clearance of prothrombin antigen–antibody complexes leads to this condition, which is associated with a bleeding tendency. It responds well to steroid therapy and IVIG.[60–62]

Avascular necrosis

The association of avascular necrosis and aPL is well documented.[63,64] Up to 30% of patients with avascular necrosis have aPL. Prospective trials are lacking but treatment with warfarin showed symptomatic relief in one study.[65]

Treatment of the asymptomatic patient

In accordance with the Sapporo criteria, asymptomatic patients with aPL are not classified as definite APLS. The significance of these antibodies in the absence of clinical features is not defined. They are often present in low titres and are of the IgM type although other classes (IgG1 and IgG3) may also be present. This contrasts with high titre and IgG2 and IgG4 type of aCL present in patients with APLS. Only 10%–15% of patients with aPL develop a thrombotic complication. Avoidance of other predisposing factors for thrombosis and preventive heparin during surgical procedures have been used by some investigators.

Another subset of patients with aPL may present with one of the minor manifestations, well described in association with APLS (e.g. thrombocytopenia, livedo reticularis, arthralgias, migraine, etc.). This group does not fulfil the criteria for definite APLS.

There are no guidelines for the treatment of these patients. Low dose aspirin has been used as the therapy of choice in symptomatic patients. Hydroxychloroquine, LMWH and warfarin are often added in patients with other risk factors.

REFERENCES

1 Conley CL, Hartmann RC. A hemorrhagic disorder caused by circulating anticoagulant in patients with disseminated lupus erythematosus. *J Clin Invest* 1952;**31:**621–2.
2 Bowie EJW, Thompson JH Jr, Pascuzzi CA, Owen CA Jr. Thrombosis in SLE despite circulating anticoagulants. *J Lab Clin Med* 1963;**62:**416–30.
3 Harris EN, Gharavi AE, Boey ML, Patel BM, Mackworth-Young CG, Loizou S, *et al*. Anticardiolipin antibodies: Detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. *Lancet* 1983;**2:**211–14.
4 Love PE, Santoro SA. Antiphospholipid antibodies: Anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. Prevalence and clinical significance. *Ann Intern Med* 1990;**112:**682–98.
5 Asherson RA, Khamashta MA, Ordi-Ros J, Derksen RH, Machin SJ, Barquinero J, *et al*. The 'primary' antiphospholipid syndrome: Major clinical and serological features. *Medicine (Baltimore)* 1989;**68:**366–74.
6 Wahl DG, Guillemin F, de Maistre E, Perret-Guillaume C, Lecompte T, Thibaut G. Meta-analysis of the risk of venous thrombosis in individuals with antiphospholipid antibodies without underlying autoimmune disease or previous thrombosis. *Lupus* 1998;**7:**15–22.
7 Saraya AK, Rai R, Saxena R, Singh RR, Padmakumar K, Malaviya AN. Coagulation abnormalities in systemic lupus erythematosus. *Indian J Med Res* 1989;**90:**335–40.
8 Padmakumar K, Singh RR, Rai R, Malaviya AN, Saraya AK. Lupus anticoagulants in systemic lupus erythematosus: Prevalence and clinical associations. *Ann Rheum Dis* 1990;**49:**986–9.
9 Saluja S, Kumar A, Khamastha M, Hughes GRV, Malaviya AN. Prevalence and clinical associations of anticardiolipin antibodies in patients with systemic lupus erythematosus in India. *Indian J Med Res* 1990;**92:**224–7.
10 Shrivastava A, Das SK, Kumar A, Das V, Sircar AR. A clinical study of antiphospholipid syndrome. *J Indian Rheumatology Assoc* 1998;**6:**13–17.
11 Uppal SS, Achutan K, Kotte VK, Saini JS. A study to assess the prevalence and thrombotic clinical spectrum of patients with procoagulant antiphospholipid antibodies. *J Indian Rheumatology Assoc* 1998;**6:**29–34.
12 Shrivastava A, Dwivedi S, Aggarwal A, Misra R. Prevalence of anticardiolipin and beta-2 glycoprotein 1 antibodies in patients with suspected primary antiphospholipid syndrome: A preliminary report. *J Indian Rheumatology Assoc* 2001;**9:**20–22.
13 Arnout J. Antiphospholipid syndrome: Diagnostic aspects of lupus anticoagulants. *Thromb Haemost* 2001;**86:**83–91.
14 Rand JH. The antiphospholipid syndrome. *Annu Rev Med* 2003;**54:**409–24.
15 Meroni PL, Raschi E, Testoni C, Tincani A, Balestrieri G. Antiphospholipid antibodies and the endothelium. *Rheum Dis Clin North Am* 2001;**27:**587–602.
16 Meroni PL, Raschi E, Camera M, Testoni C, Nicoletti F, Tincani A, *et al*. Endothelial activation by aPL: A potential pathogenetic mechanism for the clinical manifestations of the syndrome. *J Autoimmun* 2000;**15:**237–40.
17 Horkko S, Miller E, Dudl E, Reavem P, Curtizz LK, Zvaifler NJ, *et al*. Antiphospholipid antibodies are directed against epitopes of oxidized phospholipids. Recognition of cardiolipin by monoclonal antibodies to epitopes of oxidized low density lipoprotein. *J Clin Invest* 1996;**98:**815–25.

18 Price BE, Rauch J, Shia MA, Walsh MT, Lieberthal W, Gilligan HM, *et al*. Anti-phospholipid autoantibodies bind to apoptotic, but not viable, thymocytes in a beta 2-glycoprotein I-dependent manner. *J Immunol* 1996;**157:**2201–8.

19 Vaarala O, Palosuo T, Kleemola M, Aho K. Anticardiolipin response in acute infections. *Clin Immunol Immunopathol* 1986;**41:**8–15.

20 Manoussakis MN, Tzioufas AG, Silis MP, Pange PJ, Goudevenos J, Moutsopoulos HM. High prevalence of anti-cardiolipin and other autoantibodies in a healthy elderly population. *Clin Exp Immunol* 1987;**69:**557–65.

21 Avcin T, Ambrozic A, Kuhar M, Kveder T, Rozman B. Anticardiolipin and anti-beta (2) glycoprotein I antibodies in sera of 61 apparently healthy children at regular preventive visits. *Rheumatology (Oxford)* 2001;**40:**565–73.

22 Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, *et al*. Euro-Phospholipid Project Group. Antiphospholipid syndrome: Clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 2002;**46:**1019–27.

23 Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, *et al*. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: Report of an international workshop. *Arthritis Rheum* 1999;**42:**1309–11.

24 Wahl DG, Guillemin F, de Maistre E, Perret C, Lecompte T, Thibaut G. Risk for venous thrombosis related to antiphospholipid antibodies in systemic lupus erythematosus—A meta-analysis. *Lupus* 1997;**6:**467–73.

25 Hirsh J, Dalen J, Guyatt G. American College of Chest Physicians. The sixth (2000) ACCP guidelines for antithrombotic therapy for prevention and treatment of thrombosis. *Chest* 2001;**119**(Suppl):1S–2S.

26 Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Larfars G, Nicol P, *et al*. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism: Duration of Anticoagulation Trial Study Group. *N Engl J Med* 1995;**332:**1661–5.

27 Schulman S, Granqvist S, Holmstrom M, Carlsson A, Lindmarker P, Nicol P, *et al*. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. *N Engl J Med* 1997;**336:**393–8.

28 Derksen RH, de Groot PG, Kater L, Nieuwenhuis HK. Patients with antiphospholipid antibodies and venous thrombosis should receive long term anticoagulant treatment. *Ann Rheum Dis* 1993;**52:**689–92.

29 Rosove MH, Brewer PM. Antiphospholipid thrombosis: Clinical course after the first thrombotic event in 70 patients. *Ann Intern Med* 1992;**117:**303–8.

30 Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med* 1995;**332:**993–7.

31 Brunner HI, Chan WS, Ginsberg JS, Feldman BM. Long-term anticoagulation is preferable for patients with antiphospholipid antibody syndrome: Result of a decision analysis. *J Rheumatol* 2002;**29:**490–501.

32 Silverman E. What's new in the treatment of pediatric SLE? *J Rheumatol* 1996;**23:** 1657–60.

33 Erkan D, Yazici Y, Peterson MG, Sammaritano L, Lockshin MD. A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. *Rheumatology (Oxford)* 2002;**41:**924–9.

34 Ruiz-Irastorza G, Khamashta MA, Hunt BJ, Escudero A, Cuadrado MJ, Hughes GR. Bleeding and recurrent thrombosis in definite antiphospholipid syndrome: Analysis of a series of 66 patients treated with oral anticoagulation to a target international normalized ratio of 3.5. *Arch Intern Med* 2002;**162:**1164–9.

35 Asherson RA. The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992;**19:** 508–12.

36 Asherson RA, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, *et al*. Catastrophic antiphospholipid syndrome: Clues to the pathogenesis from a series of 80 patients. *Medicine (Baltimore)* 2001;**80:**355–77.

37 Asherson RA, Cervera R, Piette JC, Font J, Lie JT, Burcoglu A, *et al*. Catastrophic antiphospholipid syndrome: Clinical and laboratory features of 50 patients. *Medicine (Baltimore)* 1998;**77:**195–207.

38 Empson M, Lassere M, Craig JC, Scott JR. Recurrent pregnancy loss with antiphospholipid antibody: A systematic review of therapeutic trials. *Obstet Gynecol* 2002;**99:**135–44.

39 Lynch A, Marlar R, Murphy J, Darila G, Santos M, Rutledge J, *et al*. Antiphospholipid antibodies in predicting adverse pregnancy outcome. A prospective study. *Ann Intern Med* 1994;**120:**470–5.

40 Lockwood CJ, Romero R, Feinberg RF, Clyne LP, Coster B, Hobbins JC. The prevalence and biologic significance of lupus anticoagulant and anticardiolipin antibodies in a general obstetric population. *Am J Obstet Gynecol* 1989;**161:**369–73.

41 Yasuda M, Takakuwa K, Tokunaga A, Tanaka K. Prospective studies of the association between anticardiolipin antibody and outcome of pregnancy. *Obstet Gynecol* 1995;**86:**555–9.

42 Rai RS, Clifford K, Cohen H, Regan L.High prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. *Hum Reprod* 1995;**10:**3301–4.

43 Lubbe WF, Butler WS, Palmer SJ, Liggins GC. Fetal survival after prednisone suppression of maternal lupus-anticoagulant. *Lancet* 1983;**1:**1361–3.

44 Cowchock FS, Reece EA, Balaban D, Branch DW, Plouffe L. Repeated fetal losses associated with antiphospholipid antibodies: A collaborative randomized trial comparing prednisone with low-dose heparin treatment. *Am J Obstet Gynecol* 1992;**166:**1318–23.

45 Lockshin MD, Druzin ML, Qamar T. Prednisone does not prevent recurrent fetal death in women with antiphospholipid antibody. *Am J Obstet Gynecol* 1989;**160:**439–43.

46 Silver RK, MacGregor SN, Sholl JS, Hobart JM, Neerhof MG, Ragin A. Comparative trial of prednisone plus aspirin versus aspirin alone in the treatment of anticardiolipin antibody-positive obstetric patients. *Am J Obstet Gynecol* 1993;**169:**1411–17.

47 Granger KA, Farquharson RG. Obstetric outcome in antiphospholipid syndrome. *Lupus* 1997;**6:**509–13.

48 Balasch J, Carmona F, Lopez-Soto A, Font J, Creus M, Fabregues F, *et al*. Low-dose aspirin for prevention of pregnancy losses in women with primary antiphospholipid syndrome. *Hum Reprod* 1993;**8:**2234–9.

49 Elder MG, de Swiet M, Robertson A, Elder MA, Flloyd E, Hawkins DF. Low-dose aspirin in pregnancy. *Lancet* 1988;**1:**410.

50 Pattison NS, Chamley LW, Birdsall M, Zanderigo AM, Liddell HS, McDougall J. Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial. *Am J Obstet Gynecol* 2000;**183:**1008–12.

51 Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: Treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *Am J Obstet Gynecol* 1996;**174:**1584–9.

52 Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ* 1997;**314:**253–7.

53 Farquharson R, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: A randomized, controlled trial of treatment. *Obstet Gynecol* 2002;**100:**408–13.

54 Branch DW, Peaceman AM, Druzin M, Silver RK, El-Sayed Y, Silver RM, *et al*. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The Pregnancy Loss Study Group. *Am J Obstet Gynecol* 2000;**182:**122–7.

55 Triolo G, Ferrante A, Ciccia F, Accardo-Palumbo A, Perino A, Castelli A, *et al*. Randomized study of subcutaneous low molecular weight heparin plus aspirin versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. *Arthritis Rheum* 2003;**48:**728–31.

56 Galli M, Finazzi G, Barbui T. Thrombocytopenia in the antiphospholipid syndrome. *Br J Haematol* 1996;**93:**1–5.

57 Stasi R, Stipa E, Masi M, Cecconi M, Seimo MT, Oliva F, *et al*. Long-term observation of 208 adults with chronic thrombocytopenic purpura. *Am J Med* 1995;**98:**436–42.

58 Lipp E, von Felten A, Sax H, Muller D, Berchtold P. Antibodies against platelet glycoproteins and antiphospholipid antibodies in autoimmune thrombocytopenia. *Eur J Haematol* 1998;**60:**283–8.

59 Diz-Küçükkaya R, Hacihanefioglu A, Yenerel M, Turgut M, Keskin H, Nalçaci M, *et al*. Antiphospholipid antibodies and antiphospholipid syndrome in patients presenting with immune thrombocytopenic purpura: A prospective cohort study. *Blood* 2001; **98:**1760–4.

60 Galli M, Barbui T. Antiprothrombin antibodies: Detection and clinical significance in the antiphospholipid syndrome. *Blood* 1999;**93:**2149–57.

61 Vivaldi P, Rossetti G, Galli M, Finazzi G. Severe bleeding due to acquired hypo-prothrombinemia–lupus anticoagulant syndrome: Case report and review of literature. *Haematologica* 1997;**82:**345–7.

62 Hudson N, Duffy CM, Rauch J, Paquin JD, Esdaile JM. Catastrophic haemorrhage in a case of paediatric primary antiphospholipid syndrome and factor II deficiency. *Lupus* 1997;**6:**68–71.

63 Asherson RA, Liote F, Page B, Meyer O, Buchanan N, Khamashta MA, *et al*. Avascular necrosis of bone and antiphospholipid antibodies in systemic lupus erythematosus. *J Rheumatol* 1993;**20:**284–8.

64 Alarcon-Segovia D, Deleze M, Oria CV, Sanchez-Guerrero J, Gomez-Pacheco L, Cabiedes J, *et al*. Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus: A prospective analysis of 500 consecutive patients. *Medicine (Baltimore)* 1989;**68:**353–65.

65 Glueck CJ, Freiberg R, Tracy T, Stroop D, Wang P. Thrombophilia and hypofibrinolysis: Pathophysiology of osteonecrosis. *Clin Orthop* 1997;**334:**43–56.