Antiphospholipid syndrome

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Abstract

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia characterized by thrombosis (venous and/or arterial or microvascular) and/or pregnancy loss or complications in association with persistently positive antiphospholipid antibodies (aPL). Numerous other systemic manifestations are designated in the international consensus criteria (Sydney) for diagnosis of APS as features associated with APS or non-criteria features. In recent years, research into aPL has increased our understanding of the pathogenic process and encouraged improved detection of aPL. There is growing evidence that complement activation plays a key role in the pathogenesis of APS. This review outlines the key features of APS, including the diagnostic laboratory tests and their interpretation, and offers advice regarding the management of patients with APS both in the medical and obstetric settings.

Keywords Anticardiolipin antibodies; anticoagulation; antiphospholipid syndrome; complement; β2-glycoprotein-I antibodies; lupus anticoagulant; obstetric morbidity; thrombosis

What's new?

- APS ACTION is the AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION) (http://www.apsaction.org/)
- Growing evidence suggests that low-positivity aPL are implicated in recurrent miscarriages and late placenta vascular-mediated obstetric morbidity
- Complement activation may play a role in both obstetric and thrombotic manifestations of APS and the terminal complement component inhibitor, eculizumab, may be useful in patients with CAPS
- There is evidence that IgG antibodies to the epitope, arginine 39-arginine 43 of the domain I (DI) portion of anti-β2-GPI (anti-DI antibodies) are strongly associated with thrombotic risk in patients with APS
- Various new assays are in development, particularly for anti-DI and an annexin A5 resistance test.
- The RAPS trial (Rivaroxaban in AntiPhospholipid Syndrome) is assessing the use of rivaroxaban, a new-generation oral anticoagulant, in thrombotic APS (http://www.controlled-trials.com/ISRCTN68222801)

Antiphospholipid syndrome (APS) is characterized by thrombosis (venous and/or arterial or microvascular) and/or pregnancy loss or morbidity in association with persistent positivity of a heterogeneous group of autoantibodies known as antiphospholipid antibodies (aPL). The international consensus criteria (Sydney) for APS were designed for scientific clinical studies, but these clinical and laboratory diagnostic criteria can be applied to diagnosis of APS in routine clinical practice. The primary targets of aPL are phospholipid-binding proteins, although antibodies directed against phospholipids and other proteins also occur. One or more of the non-criteria features of APS, such as heart valve disease, livedo reticularis (LR), thrombocytopenia, and nephropathy, may present in association with thrombosis and/or pregnancy morbidity or as isolated features. In the laboratory, the usual diagnostic tests for aPL are:

- lupus anticoagulants (LA), which cause prolongation of *in vitro* phospholipid-dependent clotting assays (e.g. activated partial thromboplastin time, dilute Russell's viper venom time [DRVVT]), which are corrected by the addition of excess phospholipid (e.g. from platelets)
- anticardiolipin antibodies (aCL) of immunoglobulin (Ig) G and IgM classes, which are determined by enzyme-linked immunosorbent assay (ELISA) and should be moderate or high positivity (i.e. exceeding 40 IgG phospholipid units (GPL) or IgM phospholipid units (MPL), or exceeding the 99th percentile, which is the cut-off beneath which aCL values lie in normal individuals for 99% of the time)
- anti-β2-glycoprotein-I (β2-GPI) antibodies of IgG and IgM class detected by ELISA that should be moderate or high positivity (>the 99th percentile).

Persistently positive aPL is defined as the presence of one or more of the antibodies defined above on two or more occasions at least 12 weeks apart.[1]

Introduction

The prevalence of aPL in the form of LA, aCL and anti-β2-GPI, based on single-point prevalence in epidemiological studies, is approximately 1–3.5% of healthy individuals.[2] The prevalence increases in the elderly and in those with chronic disease.[3] Clinical associations of aPL are listed in Table 1. APS has been described as secondary if there is an associated autoimmune disorder, but the international consensus classification advises against using the term 'secondary' on the basis that the relationship between APS and systemic lupus erythematosus (SLE) may not be simply causal.[1] Several studies have shown that the prevalence of aPL in SLE patients is variable (15–86%). The frequency of antibody positivity is likely to be around 30%, with the wide variation found in the literature explained by study variations, ethnicity and

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Clinical associations of antiphospholipid antibodies

Conditions associated with production of aPL

- Systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Behçet's disease, temporal arteritis, Sjögren's syndrome
- Infections — HIV, varicella, hepatitis C, syphilis, malaria, leprosy
- Drugs — phenothiazines, procainamide, phenytoin, quinidine, hydralazine
- Lymphoproliferative disease (lymphoma, paraproteinaemia)

Clinical manifestations in patients with aPL

- Cardiovascular — venous/arterial thromboembolic disease, valvular heart disease, sterile endocarditis with embolism
- Obstetric — recurrent miscarriage, intrauterine fetal death (IUFD), stillbirth, early severe pre-eclampsia, HELLP* syndrome, placental insufficiency, prematurity, intrauterine growth restriction (IUGR)
- Neurological — cerebral ischaemic events, chorea, dementia, psychiatric disorders, transverse myelopathy, seizures, Guillain—Barré syndrome, Sneddon's syndrome
- Haematological — autoimmune thrombocytopenia, autoimmune haemolytic anaemia
- Dermatological — livedo reticularis

aPL, antiphospholipid antibodies; *HELLP, haemolysis, elevated liver enzymes and low platelets.

Table 1

extent of autoimmune disease activity. Up to an estimated 40% of patients with SLE and aPL will eventually develop clinical features consistent with APS, whereas under 5% of patients with APS will develop SLE. Well-designed multi-centre prospective studies involving large numbers of patients with APS are lacking. APS ACTION (AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking; http://www.apsaction.org/) has set up a large-scale, international multi-centre clinical registry specifically designed for patients with persistently positive aPL. The primary objective of this registry is to define the natural course of at least 2000 patients over 10 years.[4]

Pathogenesis

Animal studies suggest that aPL is directly prothrombotic, and a number of mechanisms for aPL-mediated thrombosis and pregnancy loss or complications have been proposed.[5,6] Evidence also suggests that altered regulation of complement may play a key role in the development of pregnancy loss or complications and thrombosis in APS.

Proposed mechanisms of aPL-mediated thrombosis and pregnancy complications are listed in Table 2. The clinical significance of any one or more of these hypotheses remains unclear and reflects the likely multifactorial complex nature of this condition, as is generally the case in acute thrombosis. Despite the persistent presence of aPL in the systemic circulation, thrombotic events occur only occasionally, suggesting that presence of aPL alone may not be sufficient to cause thrombosis and/or pregnancy failures. The development of aPL is probably only one step towards the development of APS, and it is likely that other factors play a role. Such 'second hits' or 'triggers' may tip the thrombotic/haemostatic balance in favour of a prothrombotic state, and include infection, endothelial injury, and other non-immunological procoagulant factors.[6] The patient's genetic make-up, in relation to candidate genes for inflammatory mediators, may also be a critical variable for the development of clinical APS manifestations. Data from several studies and systematic reviews suggest that positive LA are a stronger risk factor for the development of thrombosis than are aCL or anti-β2-GPI. In addition, a first thromboembolic event is considered rare in aPL carriers but the risk in those who are 'triple positive' for all of LA, aCL and anti-β2-GPI appears to be considerable (cumulative incidence after 10 years 37%).[6]

Among anti-β2-GPI antibodies it is those that bind specifically to a limited epitope on domain 1 of the protein (Arg39-Arg43) that appear to be most strongly associated with thrombosis.[7] Both retrospective and prospective studies suggest that weakly positive aPL (95th—99th percentile of GPL or MPL of either aCL or anti-β2-GPI or both) are implicated in recurrent miscarriage.[8] A retrospective cohort study has demonstrated that over 50% of women with clinical features of obstetric APS, but no thrombosis, had low-positivity aCL and/or anti-β2-GPI in the absence of LA.[9] Furthermore, clinical studies have demonstrated that persistent weakly positive aCL in untreated pregnancies of women with recurrent miscarriage and aPL were associated with a >90% fetal loss rate, and with significantly improved pregnancy outcome following treatment with low-dose aspirin or heparin/low molecular weight heparin (LMWH) and aspirin.[10]

Clinical features

Thrombosis

The association between aPL and thrombotic events is well established. Venous thromboembolism (VTE) is a common disorder, occurring in 1 per 1000 people per year[11] with APS accounting for approximately 10% of these acute VTE cases. The deep veins of the lower limbs is the most common site of venous thrombosis in APS and nearly half of patients presenting with deep venous thrombosis (DVT) also have pulmonary embolism. The most frequent site of arterial occlusion is in the cerebral vasculature, which may be thrombotic or embolic, resulting in transient cerebral ischaemic attacks (TIAs) and/or stroke. It has been observed that 13% and 7% of patients with ischaemic stroke and TIAs, respectively, are aPL positive, and that more than 20% of strokes in patients younger than 45 years of age are probably associated with APS. However, data relating to a possible association between aPL and stroke recurrence in older patients are conflicting. The British Committee for Standards in Haematology (BCSH) guidelines recommends that young adults (<50 years) with ischaemic stroke should be screened for aPL (level 2C).[3] Any site of the vascular system can be affected. Concomitant presence of other risk factors for thrombosis (e.g. pregnancy and surgery) increases the risk of thrombosis in APS patients, as do co-existent heritable thrombophilias such as factor V Leiden.

Neurological manifestations

Ischaemic stroke due to arterial thrombosis is the most common neurological manifestation (>50% of CNS complications) in APS.

Proposed mechanisms of aPL-mediated thrombosis and pregnancy complications

Mechanisms of aPL-mediated thrombosis

Interference with the components of the coagulation cascade
- Inhibition of protein C activity (acquired protein C resistance)
- Inhibition of protein S cofactor activity
- Inhibition of antithrombin activity
- Inhibition of protein Z pathway
- Activation of contact pathway
- Inhibition of tissue factor pathway inhibitor
- Activation of factor XI
- Induction of platelet aggregation
- Induction of microparticle formation
- Anti-β2-GPI-thrombin interaction

Impairment of fibrinolysis
Complement activation
Cell interactions
- Induction of proinflammatory phenotype on endothelial cells
- Induction of procoagulant activity of activity on endothelial cells and monocytes

Oxidant-mediated endothelial injury
Disruption of annexin V shield
ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type 1 motif, member 13) dysfunction

Mechanisms of aPL-mediated fetal loss or complications

Intraplacental thrombosis
Complement activation
Inflammation
Inhibition of syncytium-trophoblast differentiation
Disruption of annexin-V shield

Table 2

Recurrent stroke can lead to multi-infarct dementia. aPL have also been linked to Sneddon's syndrome (recurrent stroke and livedo reticularis). The revised international consensus (Sydney) classification criteria do not include other neurological manifestations that may be associated with aPL, such as cognitive dysfunction, headache or migraine, multiple sclerosis-like disease, transverse myelitis, epilepsy, psychiatric disorders, ocular symptoms or chorea. Headache is one of the neurological manifestations most often described in patients with APS, presenting as either chronic headache or episodes of migraine, although there are conflicting data on a possible relationship between migraine and aPL.[5]

Pregnancy morbidity

There is strong evidence linking aPL to recurrent pregnancy loss (RPL) and late pregnancy complications. Evidence suggests that fetal death is the most specific for APS, and recurrent early miscarriages may be the most sensitive manifestations of obstetric APS. However, the most common cause of early miscarriages is chromosomal abnormality. Persistent aPL are seen in about 15% of women with recurrent miscarriage in the first or second trimester. In these women, the fetal loss rate can be up to 90% without pharmacological treatment. Clinical criteria for obstetric APS defined in the international consensus (revised Sapporo) criteria include:

- recurrent miscarriages (three or more consecutive miscarriages), with the majority occurring after detection of embryonic/fetal heart activity
- one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or
- one or more premature births of a morphologically normal neonate before the 34th week of gestation associated with eclampsia/severe pre-eclampsia or recognized features of placental insufficiency.

Pregnancy complications such as placental abruption, late premature birth, two unexplained miscarriages and two or more unexplained *in vitro* fertilization failures, with no history of previous documented thrombosis are now being recognized as non-criteria obstetric morbidity associated with APS (OMAPS).[8,12] There is growing evidence, detailed above, that low-positivity aPL may be responsible for a number of cases with isolated obstetric complications.

Catastrophic APS (CAPS)

Catastrophic APS (CAPS) is a rare but potentially fatal variant of APS, which is characterized by sudden extensive microvascular thrombosis leading to multi-organ failure. Widespread complement activation may play a role. Although less than 1% of patients with APS develop CAPS, currently the outlook for these patients is very poor with mortality rate as high as 50% even with intensive treatment with currently used empirical therapies, discussed below.

Seronegative antiphospholipid syndrome

Seronegative APS is defined as patients with clinical manifestations highly suggestive of APS but persistently negative conventional aPL. Some of these patients may have non-criteria antibodies that may be relevant to APS, such as phosphatidylethanolamine, phospholipid-binding plasma proteins, phospholipid–protein complexes and anionic phospholipids other than cardiolipin. There is evidence that IgG antibodies to the epitope, arginine 39–arginine 43, of the domain I (DI) portion of anti-β2-GPI (anti-DI antibodies) are associated with APS. In addition to

current standard aPL antibody assays, various new assays are in development, particularly for anti-DI and an annexin A5 resistance test.

Diagnosis

Accurate diagnosis of APS is fundamental to optimal management of affected individuals. Patients with APS can present to various clinical specialists including haematologists, rheumatologists, obstetricians, general physicians and dermatologists.

What criteria are used to make the diagnosis at present?

Table 3 illustrates the criteria for APS based on the 2006 Sydney update of the Sapporo classification. The original purpose of these criteria was to achieve agreement in scientific clinical studies, although they are also useful for assisting diagnosis in routine clinical practice. Given that thrombotic disease, pregnancy loss and transient aPL positivity are common, it is important to address other causes of thrombosis and miscarriage during the initial evaluation of suspected APS. A careful clinical history is paramount as well as a detailed drug history since substances such as phenothiazines, phenytoin, hydralazine and β-adrenoceptor blockers are associated with aPL positivity.

Who should be tested for APS?

Table 4 lists the indications for aPL testing, which should be undertaken in a specialized laboratory that perform these assays regularly. Samples for LA should be taken with minimal venous stasis and platelet-poor plasma should be prepared within 1 hour of blood collection. Inadequate attention to blood sampling and preparation may result in a false-negative result for LA. Anticoagulation may interfere with laboratory diagnosis of LA; however, in certain specialized laboratories, aPL testing can be performed while the patient is taking anticoagulant treatment. Strategies include the use of the DRVVT where the international normalized ratio (INR) is <3.0, or the use of an alternative coagulation test employing a reagent that is less sensitive to the effects of warfarin (the Taipan snake venom time).

Diagnostic criteria for antiphospholipid syndrome[a]

Clinical criteria

- Vascular thrombosis — one or more episodes of arterial, venous or small vessel thrombosis in any tissue or organ (confirmed by imaging or histopathology)
- Recurrent pregnancy loss (1 after >10 weeks' gestation, or 3 after <10 weeks' gestation) or one or more premature births due to pregnancy complications

Laboratory criteria

- Lupus anticoagulant in plasma on two occasions at least 12 weeks apart
- Anticardiolipin antibodies of IgG and/or IgM isotype on two occasions at least 12 weeks apart
- Anti-β2-GPI antibody of IgG or IgM isotype on two occasions at least 12 weeks apart

Ig, immunoglobulin; GPI, glycoprotein-I

[a] Antiphospholipid syndrome is considered to be definitely present when at least one clinical criterion and one laboratory criterion are met

Table 3

Indications for antiphospholipid antibody testing

Consider testing in all patients with:

- Unprovoked proximal DVT or PE especially in the young or in those with thrombosis at unusual sites
- Recurrent thrombosis
- Young adults (<50 years) with ischaemic stroke
- Systemic lupus erythematosus or those with autoimmune disease and thrombosis
- Recurrent pregnancy loss or pregnancy complications with premature birth
- Unexplained thrombocytopenia
- Livedo reticularis

DVT, deep vein thrombosis; PE, pulmonary embolism

Table 4

Management

The BCSH published revised guidelines on the diagnosis and management of APS in 2012.[3] The American College of Chest Physicians (ACCP) guidelines includes advice on the management of patients with APS and a history of pregnancy morbidity.[13]

Asymptomatic aPL

Prophylactic intervention for the prevention of primary thrombosis in asymptomatic individuals with persistent aPL is not supported by available evidence. However, it is prudent to observe general thrombotic risk reduction measures (e.g. avoidance of smoking, oestrogen-containing oral contraception and hormone replacement therapy) and give short-term heparin prophylaxis during high-risk periods (surgery, periods of immobilization and hospitalization). A prospective, randomized clinical trial showed that prophylactic low-dose aspirin is ineffective for the prevention of thrombosis in individuals with asymptomatic aPL.[14] Whether primary prophylaxis with antithrombotic treatment is useful for some subsets of aPL patients at particularly high risk of thrombosis, such as those with SLE or with specific patterns of aPL positivity, remains to be established.

Venous thromboembolism and stroke

The conventional initial management of VTE involves standard therapy with LMWH followed by oral anticoagulation. The current consensus is indefinite anticoagulation with vitamin K antagonists (VKA) such as warfarin in patients with venous or arterial thrombosis. The optimal intensity of long-term anticoagulation must balance the risk of thrombosis against that of bleeding. The reported annual incidence of major bleeding in patients on warfarin with an INR range of 2.0—3.0 was estimated to be between 1.1% and 2.3% in selected patients, but these figures may be higher in unselected populations. The risk of fatal bleeding is 0.25%.[15] At present, many clinicians use long-term standard-intensity anticoagulation (target INR 2.5) for patients with a first episode of VTE in patients with APS, and high-intensity anticoagulation (target INR 3.5) for patients with APS-related stroke.[16—18] Warfarin treatment in APS is problematic.

In addition to its numerous drug and food interactions, monitoring of warfarin effects in patients with aPL can be complicated by the variable responsiveness of thromboplastin reagents (used to determine prothrombin time and calculate INR) to LA, which may in turn influence the validity of the prothrombin time/INR in monitoring oral VKA treatment in patients with APS. Furthermore, LA detection in patients taking warfarin may be problematic because of prolonged phospholipid-dependent clotting times. The RAPS (Rivaroxaban in AntiPhospholipid Syndrome) trial is assessing the use of rivaroxaban, a new-generation oral anticoagulant, in thrombotic APS (http://www.controlled-trials.com/ISRCTN68222801).

Other risk factors associated with thrombosis such as smoking, hypertension, diabetes mellitus and hypercholesterolaemia should be addressed adequately and exercise encouraged to all patients. Some thrombotic APS patients develop recurrent thrombotic events despite therapeutic anticoagulation. Consensus guidelines support the use of hydroxychloroquine and statins as adjuvant therapy to anticoagulation in APS patients with recurrent thrombosis despite anticoagulation.[19]

Non-criteria manifestations of APS

Patients with aPL positivity may experience other manifestations including thrombocytopenia, cardiac valve disease (CVD), aPL nephropathy, skin ulceration or cognitive dysfunction, which are collectively referred to as non-criteria manifestations of APS. An open-label phase II study of rituximab for non-criteria manifestations of antiphospholipid syndrome (RITAPS) suggested that rituximab may be effective in controlling some, but not all non-criteria manifestations of APS. The most dramatic clinical response was improvement in skin ulcers. There was no notable change in the aPL profile with rituximab treatment in this cohort.[20]

Pregnancy morbidity

All women with obstetric APS should be managed in a multidisciplinary setting involving at least obstetricians and haematologists. The recommended treatment in women who experience recurrent miscarriage (and no history of thrombosis) associated with aPL is a combination of low-dose aspirin and LMWH (ACCP 2012).[13] The evidence for this is driven primarily by the results of a single randomized, controlled trial in which aspirin was used as the control. While some studies suggest aspirin alone or even supportive care only, *in vitro* data support an adjunctive role for heparin in this situation. The ideal duration of such therapy has not been determined, but in women with miscarriage about 25% of treated pregnancies are associated with late obstetric complications. In these patients, placental thrombosis may be contributory, and it is reasonable to continue LMWH to 38 weeks' gestation, and aspirin until delivery. LMWH thromboprophylaxis for 6 weeks post-partum is advisable in women considered to be at increased risk (e.g. presence of LA, moderate/high positive anti-β2-GP1 or aCL, age >35 years or high body mass index).

Warfarin is contraindicated in early pregnancy due to its teratogenicity. In addition, fetal intracerebral haemorrhage can occur at any time during gestation. Women taking long-term oral anticoagulation must be advised that warfarin should be stopped as early as possible and before 6 weeks' gestation. Thrombotic risk is increased during pregnancy, and women with thrombotic manifestations of APS require careful anticoagulation, which should be individualized.

Catastrophic antiphospholipid syndrome

The management of this rare condition is based on anecdotal and case reports that suggest the following agents may be beneficial: anticoagulation, mainly parenteral, intravenous immunoglobulin, plasma exchange and immunosuppressive therapy, including high-dose corticosteroids, cyclophosphamide, rituximab and the terminal complement component inhibitor eculizumab.[21]

Eculizumab is being evaluated in a phase II clinical trial for its ability to prevent CAPS after renal transplantation in patients with a previous history of CAPS (http://clinicaltrials.gov/show/NCT01029587).

Conclusions

The pathophysiology of thrombosis in APS is multifactorial and not fully defined. Current anticoagulant treatment with VKA in thrombotic APS is problematic and insufficient for at least some patients with APS who develop recurrent thrombosis despite therapeutic anticoagulation. Non-thrombotic manifestations of APS are not addressed by treatment with anticoagulation alone. Further studies to investigate the pathophysiology of APS as well as ongoing and future clinical studies will further define APS, and its course and optimal management. ◆

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Practice points

- Based on current evidence, thromboprophylaxis with aspirin and or/coumarins is not recommended for individuals positive for aPL, who are asymptomatic. However, it is prudent to observe general thrombotic risk reduction measures and give short-term heparin prophylaxis during high-risk periods
- The use of primary prophylaxis with antithrombotic treatment in some subsets of aPL patients at particularly high risk of thrombosis, such as those with SLE or with specific patterns of aPL positivity (triple positivity), remains to be established. In this context, the risk of a first thromboembolic event appears to be considerable (cumulative incidence after 10 years 37%) in individuals who are 'triple positive' for all of LA, aCL and anti-β2-GPI
- At present, many clinicians use long-term standard-intensity anticoagulation (target INR 2.5) for patients with a first episode of VTE in patients with APS
- The optimal antithrombotic treatment and intensity of anticoagulation following arterial thrombosis in patients with APS is controversial and The Task Force at the 13th International Congress on Antiphospholipid Antibodies recommended that patients with definite APS and arterial thrombosis should be treated with warfarin at an INR >3.0 or with combined antiaggregant-anticoagulant (INR 2.0–3.0) therapy
- Consensus guidelines support the use of hydroxychloroquine and statins as adjuvant therapy to anticoagulation in APS patients with recurrent thrombosis despite anticoagulation
- The recommended treatment for women with no history of thrombosis who experience recurrent miscarriage associated with aPL is a combination of low-dose aspirin and LMWH during future pregnancies (ACCP 2012)