Antiphospholipid syndrome

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Abstract

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia characterized by venous or arterial thrombosis, and/or pregnancy loss or complications in the presence of persistently positive antiphospholipid antibodies. Patients can also develop other organ involvement, referred to as non-criteria manifestations, including livedo reticularis, thrombocytopenia and nephropathy. Non-thrombotic inflammatory mechanisms are increasingly identified in the pathogenesis of APS, alongside a recognition that obstetric APS may be a specific subset of APS. Treatment remains focused on lifelong anticoagulation and prevention of further thrombosis or obstetric complications. Identification of novel mechanisms is, however, leading the development of diagnostic tests and more targeted therapies to improve disease management.

Keywords β2-Glycoprotein-1 antibodies; anticardiolipin antibodies; anticoagulation; antiphospholipid syndrome; complement; lupus anticoagulant; MRCP; obstetric morbidity; thrombosis

Key points

- Antiphospholipid syndrome (APS) is an appreciable cause of unprovoked thrombosis and acquired pregnancy morbidity
- Obstetric and thrombotic APS have distinct phenotypes and mechanisms
- Triple antiphospholipid antibody positivity confers the highest risk of clinical events
- Non-thrombotic manifestations are increasingly recognized
- Current treatment remains focused on anticoagulation
- Emerging evidence supports the use of direct oral anticoagulants in venous thrombosis, and other non-anticoagulant therapies in refractory APS

Introduction

Clinical manifestations of venous or arterial thrombosis and/or certain forms of pregnancy loss in the presence of persistently positive antiphospholipid antibodies (aPLs) are required to classify antiphospholipid syndrome (APS) according to international criteria (Table 1).[1] These criteria, primarily intended to create well-defined cohorts for research studies, are routinely applied in clinical practice to aid diagnosis. Current criteria aPL tests include detection of: anticardiolipin antibodies (aCLs) and/or anti-β2-glycoprotein I (β2GPI) antibodies by enzyme-linked immunosorbent assay (ELISA); and/or positive lupus anticoagulant (LA) assay by prolongation of *in vitro* phospholipid-dependent clotting assays that can be corrected by addition of excess phospholipid.

Epidemiology

Estimates of aPL in the general population vary around 1–5%, with increased prevalence: in elderly patients; with various medications; in infections (including human immunodeficiency virus, varicella, hepatitis C, syphilis, malaria and leprosy); in lymphoproliferative disorders; and in other autoimmune rheumatic diseases (ARDs), principally systemic lupus erythematosus (SLE). The precise prevalence of APS is, however, unknown. The AntiPhospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) systematically analysed published studies to produce estimates of aPL prevalence of 6% in pregnancy morbidity, 10% in deep vein thrombosis (DVT), 11% in myocardial infarction, 14% in stroke and 17% in stroke in individuals <50 years of age.

An observational European study (Euro-Phospholipid project) defined the characteristics of 1000 patients with APS.[2] Of these, 82% were female. Most (53.1%) had primary APS in the absence of another disease; the remainder had APS in association with another ARD, most commonly SLE. Although these cases were originally defined as secondary APS, this distinction is now considered less useful, and current classification criteria recommend that any associated disorder be reported as ARD-associated APS. Although aPLs are found in up to 40% of patients with SLE, only 40% of those patients develop APS. A more severe variant with widespread microvascular thrombosis and high morbidity/mortality – catastrophic APS (CAPS) – occurs in 1% of patients with APS.

Pathogenesis

Animal models and *in vitro* studies provide direct evidence that aPLs cause thrombotic and obstetric APS (OAPS) manifestations.[3] One of the main distinguishing properties of pathogenic aPLs is their binding to β2GPI, a protein composed of five regions called domains (D) I–V that contains an important epitope for pathogenic aPL on DI, particularly the region from arginine (Arg) 39 to Arg43. Other antibodies identified in APS include those directed against prothrombin, protein C, protein S, annexin V and factor Xa. Interestingly, antibodies directed against β2GPI and prothrombin have shown to be responsible for the prolongation of clotting times observed *in vitro* in LA tests.

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Classification criteria for APS

Clinical criteria:

- Vascular thrombosis
  - Arterial, venous or small vessel thrombosis in any tissue or organ (excluding superficial thrombosis), confirmed by appropriate imaging or histopathology
- Pregnancy morbidity – at least one of the following:
  - One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation
  - One or more premature births or a morphologically normal neonate before the 34th week of gestation owing to eclampsia or severe pre-eclampsia or placental insufficiency
  - Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with hormonal, chromosomal or maternal anatomic causes excluded

Laboratory criteria: any must be present on two or more occasions at least 12 weeks apart:

- LA present in plasma, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
- IgG and/or IgM isotype aCL present in medium to high titre (i.e. >40 IgG phospholipid units or IgM phospholipid units) as measured by standard ELISA
- IgG and/or IgM isotype anti-β2GP1 antibody in serum or plasma, present in medium/high titre (e.g. >99th centile)

To fit the classification, one feature from each set of the clinical and laboratory criteria is required. The classification criteria are primarily a research tool, and do not include all clinical features or manifestations.

Table 1

In contrast to this *in vitro* anticoagulant phenomenon, pathogenic aPLs have been shown to have inflammatory, thrombotic and adverse obstetric effects in various animal models and on various target cells, including monocytes, endothelial cells, neutrophils and trophoblast cells; this leads to recruitment of cell surface receptors, perturbation of intracellular signalling pathways and upregulation of proinflammatory and procoagulant factors. These effects are mediated through interactions with components of the coagulation and/or complement cascade as well as cell surface interactions between aPL–β2GPI complexes cross-linking various receptors on different cell types (Figure 1).

A 'two-hit' hypothesis has been proposed: the first hit is an aPL-induced prothrombotic/inflammatory state, and the second is exposure to an acute precipitating event such as surgery, immobilization, exogenous oestrogen or pregnancy. Interestingly, pregnancy does not serve purely as a precipitating prothrombotic state, because comparison of products of conception from aPL-positive and aPL-negative women with recurrent early miscarriage demonstrates a specific defect in decidual endovascular trophoblast invasion in OAPS and shows placental infarction is not unique to APS.

Experimental evidence is increasingly implicating non-thrombotic mechanisms in the pathogenesis of OAPS by aPL-mediated complement activation, inflammation and impairment of placental development and function (Figure 1). In addition, clinical data from the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS) on 247 patients with OAPS demonstrated that progression to thrombosis and SLE is low compared with patients with thrombotic APS[4]; this lends credence to the hypothesis that OAPS is a specific subset of APS.

Clinical features

Although vascular thrombosis and certain adverse pregnancy outcomes are the main clinical features of APS, other non-classification criteria clinical features are increasingly recognized (Table 2) and indicate the variety of non-thrombotic effects of aPL. For instance, in the Euro-Phospholipid project, the most common presenting non-criteria features were thrombocytopenia (21.9%), livedo reticularis (20.4%), superficial thrombophlebitis (9.1%) and haemolytic anaemia (6.6%).

Vascular thrombosis

Thrombotic events, most commonly venous events in the lower limbs, are the hallmark of APS. The presence of aPL increases the risk of venous thrombosis in patients with SLE 2-fold for aCL and 6-fold for LA, compared with healthy populations. In patients without an underlying ARD, venous thrombotic risk is increased 1.5-fold for aCL and up to 10-fold for LA, while arterial thrombosis is increased 3-fold (aCL) and 4- fold (LA). The risk of recurrent thrombosis or thromboembolism can further increase in patients with triple positivity to LA, aCL and anti-β2GPI antibodies. Vascular events in the Euro-Phospholipid project included DVT (32%), stroke (13.1%), pulmonary embolism (PE; 9.0%), transient ischaemic attack (7.0%) and amaurosis fugax (2.8%).

Given that aPL positivity is found for 17% of strokes in patients <50 years of age (compared with 0.7% of control participants), the British Society of Haematology guidelines on investigation and management of APS recommend that anyone <50 years of age presenting with an ischaemic stroke should be screened for aPL.[5]

Obstetric manifestations

Table 1 shows the current classification of OAPS. Recurrent miscarriages are a hallmark of APS. In the Euro-Phospholipid project, the most common fetal complications were early fetal loss (35.4%), late fetal loss (16.9%) and premature birth (10.6% of live births). The most common obstetric complications in the mother were pre-eclampsia (9.5% of pregnant women), eclampsia (4.4%), and abruptio placentae (2.0%). Similarly, recurrent miscarriage and late fetal loss were the most common complications in the EUROAPS registry. Although laboratory data from Euro-phospholipid and EUROAPS confirm associations between all criteria aPLs and pregnancy complications, the strongest association was found for LA and triple positivity.

Non-criteria manifestations

Although many multisystem manifestations of APS (Table 2) are thrombotic in nature, it is increasingly recognized that aPLs have other immune-mediated effects producing manifestations that fall outside current APS classification criteria. These non-criteria manifestations involve multiple organ systems. Patients can present with valvular heart disease, and develop a sterile endocarditis (Libman–Sacks endocarditis) that gives rise to embolic complications.

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