The General Practice Guide to Autoimmune Diseases

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The antiphospholipid syndrome

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1 Introduction

The antiphospholipid syndrome (APS) represents the most prevalent acquired thrombophilia and causes venous, arterial and small-vessel thrombosis, pregnancy loss, and preterm delivery for patients with severe pre-eclampsia or placental insufficiency. It is associated with the presence of antiphospholipid antibodies (aPL), mainly lupus anticoagulant (LA) and anticardiolipin (aCL) and anti-β2 glycoprotein-I (β2-GPI) antibodies, directed against negatively charged phospholipids (aPL) [1].

In the general population, aPL can be detected in about one in five patients who have had a stroke at less than 50 years of age. About 25 % of patients with venous thromboembolism in whom a thrombophilia test is done have aPL. In addition, 10 %–15 % of women with recurrent miscarriage are diagnosed with APS. Although foetal death is linked to APS, the overall contribution of this syndrome is uncertain. aPL are detected in 11 %–29 % of women with pre-eclampsia [1].

APS is associated with systemic lupus erythematosus (SLE) in about 35 % of the cases, 5 % of APS patients have 'lupus-like' syndrome, 5 % other immune diseases and in 55 % of the patients APS presents alone. Mean age at the onset of symptoms of APS is 31 years with a 5/1 female/male ratio [1, 2].

2 How do antiphospholipid antibodies increase the risk of vascular thrombosis and pregnancy morbidity in APS?

β2-GPI has been described as one of the major target antigens for aPL [3] and plays a pivotal role in the pathophysiology of APS. β2-GPI, a protein synthesized in the liver, circulates in plasma in a closed conformation. After a small injury, cells express phosphatidylserine on their surface which binds to β2-GPI and, as a result, its conformation changes from closed to stretched structure. The aPL will bind to β2-GPI so that this protein is then able to interact with receptors on the surface of the cells. It leads to a procoagulant state with effects on the vascular bed and placenta by means of activation of endothelial cells, monocytes and platelets

and the complement cascade. These mechanisms often act in the presence of other cardiovascular risk factors, which are present in more than 50 % of APS patients and may trigger the thrombotic event ('second hit') [3].

Lupus anticoagulant is the strongest predictor of features related to APS. The role of aCL in the absence of LA is more debated, with no associated increased risk for stroke or myocardial infarction. Isolated anti-β2-GPI is weakly associated with clinical manifestations of APS. High-risk aPL profile includes LA positivity, triple positivity (LA + aCL + anti-β2-GPI) or isolated persistently positive aCL at medium-high titers [1].

3 Criteria and non-criteria clinical manifestations in APS

The spectrum of clinical manifestations of APS is wide and the prevalence of the clinical features is highly variable [1, 2]:

1. Frequent (> 20 % of cases): deep venous thrombosis, early foetal losses (< 10 weeks), stroke, migraine, arthralgia and/or arthritis, thrombocytopenia and livedo reticularis.
2. Less common (5 %–20 % of cases): superficial thrombophlebitis in legs, skin ulcers, pulmonary embolism, transient ischaemic attack, amaurosis fugax, cognitive dysfunction, mitral or aortic valve thickening or dysfunction, myocardial infarction, haemolytic anaemia, pre-eclampsia, late foetal losses (≥10 weeks) and premature birth.
3. Unusual or rare (< 5 %): arterial thrombosis in legs, venous or arterial thrombosis in arms, subclavian or jugular thrombosis, epilepsy, multi-infarct dementia, chorea, transverse myelitis, pulmonary hypertension, diffuse alveolar haemorrhage, angina, valve vegetations, retinal artery or vein thrombosis, cutaneous necrosis, splinter haemorrhages, avascular necrosis of bone, mesenteric ischaemia, adrenal haemorrhage, Budd-Chiari syndrome, APS nephropathy, renal artery or vein thrombosis, eclampsia and placental abruption.

Thrombosis of deep limb veins (39 %) and pulmonary embolism (14 %) are the most common venous manifestations of APS, and ischaemic stroke (20 %) is the most prevalent arterial thrombotic event. SLE-related APS patients have more episodes of arthritis and livedo reticularis, and more frequently exhibit thrombocytopenia and leucopenia, although show a similar profile regarding vascular thrombosis and pregnancy morbidity when compared with those patients with non SLE-related APS [2].

4 Classification criteria for definite APS (Sydney 2006)

Although APS can involve almost any organ, only vascular thrombosis and recurrent fetal loss are included in the revised classification criteria (Sydney 2006)

[4]. Accordingly, APS is present if at least one of the clinical criteria and one of the laboratory criteria (LA, aCL and/or anti-β2-GPI) are met (Table 2). Although other clinical and laboratory features not included in revised classification criteria for APS, such as heart valve disease, livedo reticularis, nephropathy, neurological manifestations, thrombocytopenia, antiphosphatidylserine antibodies (aPS), antibodies against annexin V and vimentin/cardiolipin complex, antiphosphatidylethanolamine (aPE) antibodies, antibodies against prothrombin alone (aPT-A) and antibodies to the phosphatidylserine–prothrombin (aPS/PT) complex are undoubtedly frequent in patients with APS, the committee considered that adoption of these features as independent criteria for definite APS may decrease diagnostic specificity, even though their association with APS is recognized [4].

However, clinical manifestations of APS are highly prevalent in the general population and in many cases there is a coincidental vascular risk factor to explain the vascular event; therefore, the diagnostic value of a positive result in aPL testing may be controversial. Thus, consideration of the non-criteria manifestations of the syndrome may help to establish an accurate diagnosis and therapeutic approach. It is worth mentioning that livedo reticularis is present in about 25 % of patients and represents a physical sign that should make the clinician suspect the diagnosis of the syndrome in the appropriate clinical context [1].

The *catastrophic antiphospholipid syndrome* (CAPS) is the most severe and infrequent variant of the syndrome and is a condition characterized by multiple vascular occlusive events, usually affecting small vessels and evolving over a short period of time, together with laboratory confirmation of the presence of antiphospholipid antibodies. A diagnosis of definite CAPS must fulfil these classification criteria [1, 2]:

1. Evidence of involvement of three or more organs, systems and/or tissues.
2. Development of manifestations simultaneously or in less than a week.
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue.
4. Laboratory confirmation of the presence of antiphospholipid antibodies.

In daily clinical practice it is not unusual to find patients with clinical manifestations suggestive of APS who are persistently negative for the routinely used assays to detect LA aCL and anti-β_2-GPI. Therefore, the term *seronegative APS* (SN-APS) has been coined to include these patients with clinical features suggestive of APS who are persistently negative for aPL [4]. The profile of such patients includes the development of thrombotic events and/or pregnancy morbidity such as recurrent foetal loss, often with non-criteria APS manifestations such as livedo reticularis or thrombocytopenia, in the absence of conventional aPL.

Although APS diagnosis relies predominantly on laboratory results, where the detection of aPL is mandatory, routine screening tests (aCL, anti-β_2-GPI and LA) might miss some cases of true seropositive-APS by failing to pick up cases

Table 1. Revised classification criteria for the antiphospholipid syndrome [1].

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met:

Clinical criteria

1. *Vascular thrombosis*

   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. *Pregnancy morbidity*

   (a) One or more unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation, with normal foetal morphology documented by ultrasound or by direct examination of the foetus, or

   (b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency-, or

   (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. *Lupus anticoagulant (LA)*

   Present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis.

2. *Anticardiolipin (aCL) antibody of IgG and/or IgM isotype*

   In serum or plasma, present in medium or high titer (i.e. > 40 GPL or MPL, or > the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized Elisa.

3. *Anti-β2 glycoprotein-I antibody of IgG and/or IgM isotype*

   In serum or plasma (in titer > the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized Elisa, according to recommended procedures.

[1] Modified from *J Thromb Haemost. 2006*; 4: 295–306.

with other antibodies directed against different phospholipids or protein cofactors (non-criteria aPL), such as prothrombin, phosphatidylethanolamine, annexin V and vimentin/cardiolipin complex. Nevertheless, their main disadvantage is the lack of standardization for such assays.

5 Who should be tested for aPL

The main focus for the search for antiphospholipid antibodies should be on patients with a thrombotic event and/or with pregnancy morbidity. In addition, patients with SLE should be tested carefully for these autoantibodies, since the simultaneous presence of SLE and aPL increases the risk for thrombosis.

Most important in the diagnostic procedure of antiphospholipid antibodies is the confirmation of a positive result after 12 weeks [4]. Before this a definitive diagnosis cannot be made. Antiphospholipid antibodies are very closely associated with a variety of infections. Thus, the possibility that the patient has a current infection must be excluded. This leads to this imperative requirement to retest the initial positive detection of aPL (see Fig. 1).

6 Treatment and prognosis

Management of APS must be individualized according to the patient's clinical status and history of thrombotic events and pregnancy morbidity. The aPL profile (high or low risk), the coexistence of other thrombotic risk factors and the presence of an underlying autoimmune disease are the most important variables for planning the treatment regimen in APS patients (see Tables 2 and 3) [1, 5].

In a cohort of 1000 patients from the 'Euro-Phospholipid project' the total mortality rate during the 5-year follow-up period was 5.3 %. In addition to severe thrombotic events (i. e., myocardial infarction, stroke or the catastrophic APS), infections and haemorrhages accounted for one-third of deaths [2].

Regarding obstetric APS, with proper management with aspirin and heparin more than 70 % of pregnant women will deliver a viable live infant [1].

Patients with CAPS require intense observation and treatment, often in an intensive care unit. The mortality rate has improved due to the use, as first-line therapies, of full anticoagulation, corticosteroids, plasma exchanges and intravenous immunoglobulins [1, 2].

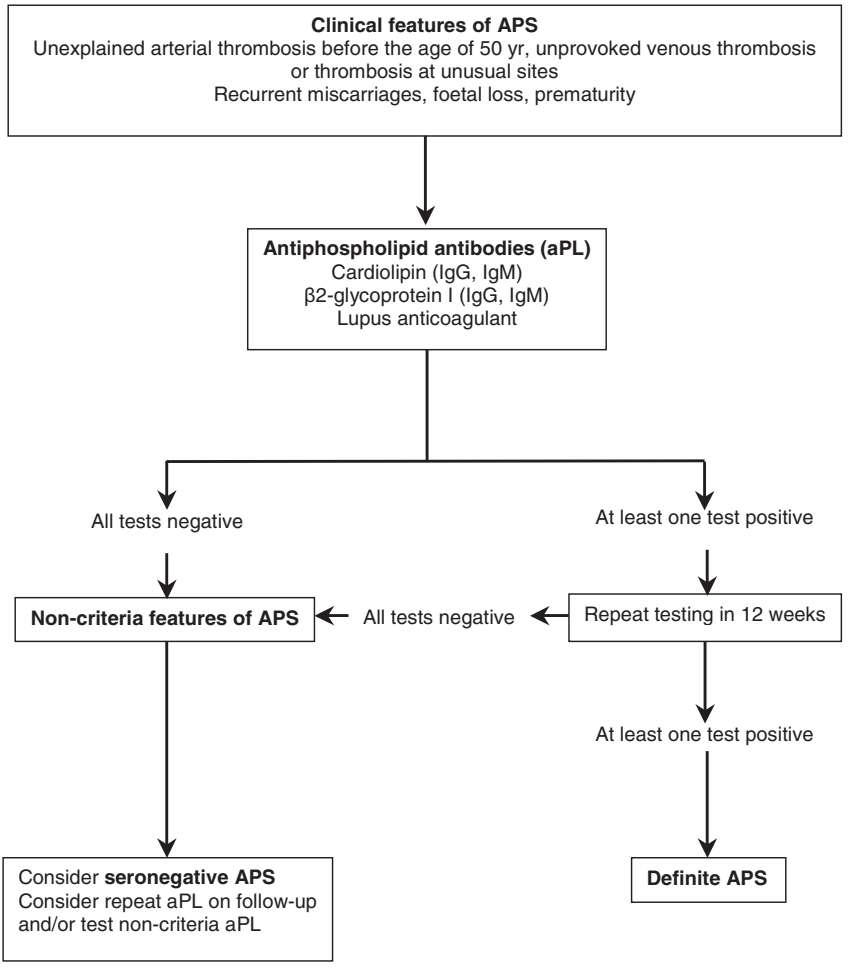

Figure 1. Algorithm for the diagnosis of the antiphospholipid syndrome (APS).

Table 2. Recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients (Modified from Lupus 2011, 20: 206–18).

aPL carriers
A strict control of cardiovascular risk factors should be accomplished in all individuals with a high-risk aPL profile*. Thromboprophylaxis with usual doses of low molecular weight heparin in high-risk situations, such as surgery, prolonged immobilization and puerperium.
Primary thromboprophylaxis in SLE patients with aPL
These patients should receive hydroxychloroquine and low-dose aspirin.
Primary thromboprophylaxis in aPL-positive individuals without SLE
Long-term primary thromboprophylaxis with low-dose aspirin in those with a high-risk aPL profile, especially in the presence of other thrombotic risk factors.
Secondary thromboprophylaxis
Patients with definite APS and a first venous event should receive oral anticoagulant therapy to a target INR 2.0–3.0. Patients with definite APS and arterial thrombosis should be treated with warfarin at an INR > 3.0 or combined antiaggregant-anticoagulant (INR 2.0–3.0) therapy, although other options such as antiaggregant therapy alone or anticoagulant therapy to a target INR 2.0–3.0 would be equally valid in this setting (lack of consensus). An estimation of the patient's bleeding risk should be performed before prescribing high-intensity anticoagulant or combined antiaggregant-anticoagulant therapy. Non-SLE patients with a first non-cardioembolic cerebral arterial event, with a low-risk aPL profile and the presence of reversible trigger factors could individually be considered candidates to treatment with antiplatelet agents.
Duration of treatment
Patients with definite APS and thrombosis should receive indefinite antithrombotic therapy. In cases of first venous event, low-risk aPL profile** and a known transient precipitating factor, anticoagulation could be limited to 3–6 months.

* High-risk: LA positivity, triple positivity (LA + aCL + anti-β2-GPI) or isolated persistently positive aCL at medium-high titers.

** Low-risk: isolated, intermittently positive aCL or anti-β2-GPI at low-medium titers.

Table 3. Usual recommended treatment of antiphospholipid syndrome during pregnancy (Modified from Lancet 2011, 376: 1498–1509).

APS without previous thrombosis and recurrent early miscarriage (< 10 weeks' gestation)
Low-dose aspirin (i.e., 100 mg/day) alone or together with LMWH (usual prophylactic doses, i.e., enoxaparin 40 mg/day)
APS without previous thrombosis and foetal death (> 10 weeks' gestation) or previous early delivery (< 34 weeks' gestation) due to severe pre-eclampsia or placental insufficiency
Low-dose aspirin plus LMWH at usual prophylactic doses
APS with previous thrombosis
Low-dose aspirin plus LMWH at usual therapeutic doses (i.e., enoxaparin 1.5 mg/kg/day)

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