

Antiphospholipid Antibody Syndrome

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Abstract

The 2006 International Consensus Statement on an Update of the Classification Criteria for Definite Antiphospholipid Syndrome has increased the time between the two laboratory studies required for diagnosis from 6 to 12 weeks. Antibody to β_2 glycoprotein 1 has been included as a criterion. Various non-criteria diagnostic clues such as livedo reticularis, heart valve disease, thrombocytopenia, renal thrombotic microangiopathy, neurological manifestations, non-criteria antibodies (IgA aCL, IgA anti- β_2 glycoprotein I) and some research laboratory-identified antibodies (antiphosphatidylserine antibodies, antiphosphatidylethanolamine antibodies, antibodies against prothrombin alone and antibodies to the phosphatidylserine–prothrombin complex) have been recognised. New concepts of pathogenesis now implicate complement activation and participation of the innate immune system upstream to thrombosis. Warfarin remains the treatment of choice for patients who have suffered thrombosis, but antiplatelet agents and heparin are other options. Target INR is 2.0–3.0.⁽¹⁾ The other drugs which are used in resistant cases are: rituximab, hydroxychloroquine, thrombin inhibitors and statins.

Introduction

The antiphospholipid syndrome (APS), first described in 1986 by Hughes, Harris, and Gharavi, is an acquired thrombophilic disorder in which autoantibodies are produced to a variety of phospholipids and phospholipid binding proteins⁽²⁾. Among the identified acquired thrombophilic states, APS is the most common. APS can be caused by the lupus anticoagulant (LA), anticardiolipin antibodies (ACA), or other antiphospholipid antibodies. The advances that have occurred in the fields of classification, pathogenesis and management of APS will be discussed.

We reviewed the English language medical literature (MEDLINE and other data at the National Library of Medicine, accessed using the PUBMED search engine, as well as the Cochrane Library) searching for last 10 years publications about recent advances in classification criteria, pathogenesis, management of antiphospholipid syndrome.

Prevalence

In young, apparently healthy control subjects, the prevalence for both lupus anticoagulant and anticardiolipin antibodies (aCL) is about 1% to 5%⁽³⁾. The prevalence increases with age, especially in elderly individuals with chronic disease⁽³⁾. The risk of thrombosis in patients with APS is estimated to range from 0.5% to 30%⁽⁴⁾. According to analysis of 1000 patients reported by the multicenter Euro-Phospholipid Project, APS syndrome is more common in women than men in about a 5:1 ratio⁽⁵⁾. Female patients also appear to more frequently demonstrate the clinical features of arthritis, livedo reticularis, and migraine, whereas males more often develop myocardial infarction, epilepsy, and lower extremity arterial thrombosis⁽⁵⁾. Although the most common mean age of onset of the clinical manifestations of APS is 31 years⁽⁵⁾, the disorder may be seen in children and older

patients as well. ACA-associated thrombosis is more common than the LA-associated thrombosis, with a ratio of 5:1⁽⁶⁾.

APS and Autoimmune diseases

Primary APS has generally been defined as the presence of aPL in patients with idiopathic thrombosis but no evidence of autoimmune disease or other inciting factor, such as infection, malignancy, hemodialysis or drug-induced aPL. The term secondary APS has been used when patients with a wide spectrum of autoimmune disorders (primarily systemic lupus erythematosus [SLE] and rheumatoid arthritis) and thrombosis are also found to have aPL. The clinical manifestations of thrombosis are similar, whether the APS is primary or secondary, and the 2006 International Consensus Statement on an Update of the Classification Criteria for Definite Antiphospholipid Syndrome eliminated the “primary” versus “secondary” distinction^(2,5). In replacing this “primary” versus “secondary” designation, the 2006 criteria designates two subgroups of APS patients—those with and those without the presence of other risk factors for arterial or venous thrombosis⁽⁷⁾.

Common autoimmune or rheumatic diseases and the percentage of affected patients with aPL antibodies:

- SLE - 25-50%
- Sjögren syndrome - 42%
- Rheumatoid arthritis - 33%
- Autoimmune thrombocytopenic purpura - 30%
- Autoimmune hemolytic anemia - Unknown
- Psoriatic arthritis - 28%
- Systemic sclerosis - 25%
- Mixed connective-tissue disease - 22%
- Polymyalgia rheumatica or giant cell arteritis - 20%
- Behcet syndrome - 20%

Pathogenesis

The family of antiphospholipid immunoglobulins is heterogeneous and targets a variety of potential antigenic targets. APS can be caused by the lupus anticoagulant (LA),

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anticardiolipin antibodies (ACA), or other antiphospholipid antibodies. Phospholipids are involved in many important processes throughout the hemostatic system. APS antibodies are associated with fetal wastage, arterial or venous thrombosis, and thrombocytopenia. There are distinct clinical, laboratory, and biochemical differences between the disorders mediated by the different antibodies.

Mechanism of Thrombosis in Antiphospholipid Syndrome (APS)

The precise mechanism whereby hemostasis is altered to induce a hypercoagulable state in APS remains unclear. Because the antibodies in APS are heterogeneous and more than one type is probably present in any given patient⁽⁶⁾, several mechanisms may be responsible for the clinical manifestations in patients who have APS. Because phospholipids are an integral part of platelet and endothelial cell surface membranes, it is expected that anti-phospholipid antibodies would have a significant effect on platelet and vascular endothelial mechanisms.

Proposed mechanisms of aPL-mediated thrombosis have included:

- Inhibition of endothelial cell prostacyclin production⁽⁸⁾
- Procoagulant effect on platelets⁽⁹⁾
- Impairment of fibrinolysis
- Interference with the thrombomodulin–protein S–protein C pathway⁽¹⁰⁾
- Induction of procoagulant activity on endothelial cells and/or monocytes⁽¹¹⁾
- Disruption of the annexin V cellular shield⁽¹²⁾
- Abnormal cytotrophoblast expression of adhesion molecules in pregnancy⁽²⁾

Even the mechanism of pregnancy loss is now in question. Findings from research in animal models of APS challenge the view that this syndrome is a non-inflammatory, thrombotic disease and provide evidence that complement activation is crucial for complications in pregnancy. These studies, in addition to providing evidence for inflammation-mediated tissue damage in placentae of patients with APS, suggest that therapy should also be directed towards preventing inflammation⁽¹³⁾. In the mouse model of APS, it has also been demonstrated that heparin (but not fondaparinux or hirudin), prevents aPL-induced complement activation. Thus, the well-demonstrated beneficial effect of heparin in APS patients is not only due to the inhibition of thrombin generation but is also due to complement inhibiting property. So, use of specific complement inhibitors in APS is an exciting area for future investigation. Furthermore, TNF α has been identified as a critical effector in APL-induced pregnancy loss, suggesting that the TNF blockade may be a potential therapy for pregnancy complications of APS.

Classification criteria

Definite Antiphospholipid Syndrome

A patient with “definite” APS must have persistent high-titer antiphospholipid antibodies (aPL) associated with a history of arterial or venous thrombosis (or both), or recurrent pregnancy morbidity^(7,14).

Laboratory criteria are well defined and require aCL IgG or IgM or lupus anticoagulant in high titers (>40 IgG

phospholipid units [GPL] or IgM phospholipid units [MPL] or >99th percentile), confirmed on repeat testing 12 weeks later^(7,14). 2006 International Criteria have included IgG and IgM antibodies to β -2-GP I, which are also highly predictive of risk for thrombosis. Patients may be found to have not only aCL or lupus anticoagulant but also other aPL or combinations^(5,7), which are not included in the criteria.

Box 1: Revised classification criteria for APS

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, occurring in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (ie, by appropriate imaging studies or histopathology). Histopathologically, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity
 - (a) One or more unexplained deaths of morphologically normal fetuses at or after the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
 - (b) One or more premature births of morphologically normal neonates 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 present in plasma*
2. aCL of IgG and/or IgM isotype in serum or plasma, present in medium or high titer*
3. Anti- β -2-GP I IgG and/or IgM isotype in serum or plasma*

*on two or more occasions at least 12 weeks apart.

Advances in classification criteria

In 1999 the first (Sapporo) consensus conference suggested the classification criteria for the antiphospholipid syndrome.⁽¹⁴⁾ In late 2004, a second (Sydney) conference considered the first 5 years of the use of these criteria and suggested revisions. The Sydney update on the classification criteria for definite APS introduced numerous modifications to the previous preliminary consensus statement. Clinical criteria are now better defined because vascular thrombosis must be diagnosed on the basis of objective criteria. Moreover, additional factors contributing to thrombosis should be assessed and APS patients should be stratified according to the presence or absence of other, inherited or acquired, contributing causes of thrombosis. These revisions, based on the argument that the syndrome is the same irrespective of the presence or absence of lupus or other rheumatic disease, changed the designations of primary and secondary APS to APS without or with associated rheumatic disease (ARD). The Sydney conference also recognized two other entities: catastrophic antiphospholipid syndrome (CAPS) and aPL with no associated symptoms. Other changes from the Sapporo criteria include extension of the interval between first and second positive test from 6 to 12 weeks, exclusion of transient positivity due to infection, addition of anti- β 2 glycoprotein I (β 2GPI), and recognition of features of the illness that can serve as diagnostic clues for individual patients but not as classification criteria for the purpose of clinical trials (cardiac valve disease, livedo reticularis, thrombocytopenia, renal thrombotic microangiopathy,

neurological manifestations, some non-criteria antibodies [IgA aCL, IgA anti-β2GPI] and some research laboratory identified antibodies such as antiphosphatidylserine antibodies, antiphosphatidylethanolamine antibodies, antibodies against prothrombin alone and antibodies to the phosphatidylserine–prothrombin complex) None of these changes alter the basic demographic findings of APS: 30–40% of SLE patients have aPL but only about 10% have APS, APS without associated rheumatic disease constitutes about half of all APS, and CAPS is rare but lethal.⁽¹⁵⁾

Box 2 Additional risk factors for thrombosis

- Age (> 55 in men, and > 65 in women)
- Risk factor for cardiovascular disease^a
- Inherited thrombophilias
- Oral contraceptives
- Nephrotic syndrome
- Malignancy
- Immobilization
- Surgery

^aHypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, BMI ≥ 30 kg/m², microalbuminuria, estimated GFR < 60 ml/min.

Clinical Spectrum

Clinical manifestations range from no symptoms to imminently life-threatening, catastrophic APS (CAPS).

Venous Thrombosis

Venous thrombosis typically presents with DVT in the lower extremities, observed in 29% to 55% of cases over a follow-up period of less than 6 years⁽¹⁶⁾. As with all cases of venous thromboembolism (VTE), more than half of the patients with symptomatic DVT have asymptomatic Pulmonary embolism. Unusual sites of venous thrombosis have included the upper extremities, intracranial veins, inferior and superior vena cava, hepatic veins (Budd-Chiari syndrome), portal vein, renal vein, and retinal vein. Thrombosis of the cerebral veins may present with acute cerebral infarction. Thrombosis of the superior sagittal sinus has also been reported.

Arterial Thrombosis

Arterial thromboses are less common than venous thromboses and occur in a variety of settings in patients with primary APS⁽¹⁶⁾. Patients with arterial thrombosis most commonly present with transient ischemic attack or stroke (50%) or myocardial infarction (23%)^(5,16). The presence of aCL is considered to be a risk factor for first stroke⁽¹⁷⁾. Arterial thrombosis in patients with APS may also involve other large and small vessels, which is somewhat unusual for other thrombophilic disorders or atherosclerotic occlusive disease. These potential arterial thromboses include thromboses of brachial and subclavian arteries, axillary artery (aortic arch syndrome), aorta, iliac, femoral, renal, mesenteric, retinal, and other peripheral arteries^(2,4,16).

Cardiac Disorders

Arterial occlusion may be either thrombotic or embolic. Premature atherosclerosis appears to be accelerated by the presence of aPL and may predispose to coronary occlusion. The revised criteria do not recommend routine performance of aPL tests in patients with coronary artery disease unless the patient's young age and lack of identifiable risk factors suggest a rare etiology. Valvular thickening, vegetations, regurgitation, premature coronary disease, myocardial infarction, dilated

diffuse cardiomyopathy, congestive heart failure, pericardial effusion, and pulmonary hypertension have all been observed⁽¹⁸⁾.

Neurologic Disorders

Primary thrombosis and embolic occlusion of cerebral arteries result in cerebral infarction, with clinical manifestations dependent upon the location and caliber of the occluded artery. Patients frequently present with strokes and TIA, and aPL, particularly lupus anticoagulants (LAC), are an independent risk factor for ischemic stroke in young adults⁽¹⁹⁾. Recurrent small strokes may contribute to a picture of multiple-infarct dementia⁽⁴⁾. Typical APS patients with stroke are relatively young and lack other classical risk factors of stroke⁽²⁰⁾. Chorea is another clinical disorder that has been strongly linked to the presence of aPL. Other central nervous system manifestations associated with aPL include migraine headache, Sneddon's syndrome, seizures, transverse myelitis, Guillain-Barre syndrome, idiopathic intracranial hypertension, cognitive dysfunction, psychosis, and optic neuritis⁽²¹⁾. The multiple sclerosis-like presentation of APS mostly reflects cognitive dysfunction and abnormal MRI. In a cross-sectional study of patients with APS, aPL without syndrome, systemic lupus erythematosus (SLE) and aPL antibody, unclassified autoimmune disease with aPL antibody, and multiple sclerosis patients with aPL antibody, it was seen that chorea, migraine, seizure, and dysarthria were more frequent in APS, while optic neuritis, bowel and bladder abnormalities, and gait disturbances were more common in multiple sclerosis. Distinctions could be made among the MRI abnormalities (in APS, abnormalities are nonenhancing with gadolinium); antibody tests are generally strongly positive in patients with APS and less so, or low-positive in patients with multiple sclerosis⁽²²⁾.

Obstetrical Disorders

Obstetrical features of APS presently include recurrent pre-embryonic and embryonic miscarriage, foetal demise. Other complications of pregnancy may also be observed, including eclampsia, intrauterine growth retardation, oligohydramninos, HELLP syndrome, and premature birth, systemic and pulmonary hypertension. Such patients also demonstrate a high rate of subsequent venous or arterial thrombosis. Pregnancy complications may occur in patients who are only later found to develop aPL⁽²³⁾.

Of all hereditary and acquired thrombophilias, APS is the most common thrombotic defect leading to fetal wastage.

Dermatologic Disorders

Dermatologic manifestations may be the first indication of APS. Histopathologically, the most common feature is noninflammatory vascular thrombosis. Clinically, patients present with livedo reticularis, necrotizing vasculitis, livedoid vasculitis, cutaneous ulcerations and necrosis, erythematous macules, purpura, ecchymoses, painful skin nodules, and subungual splinter hemorrhages. Anetoderma, discoid lupus erythematosus, cutaneous T-cell lymphoma, and disorders similar to Degos and Sneddon's syndrome are also rarely observed⁽²⁴⁾. Patients with livedo reticularis and APS frequently also have cardiac and cerebral thrombotic events, epilepsy, and migraine headaches⁽²⁵⁾.

Pulmonary

Pulmonary microthrombosis is among the most frequent arterial complications of APS. The spectrum of “antiphospholipid lung syndrome” includes thromboembolism of lung arteries, pulmonary hypertension, adult respiratory distress syndrome, postpartum syndrome, and others⁽²⁶⁾. Diffuse alveolar haemorrhage is now a recognized non-thrombotic manifestation of APS⁽²⁷⁾. Timely diagnosis of pulmonary manifestations is required because of their severity and high mortality rate.

Abdominal Manifestations

Hepatic involvement was the most common of the APS abdominal manifestations, followed by thrombotic events involving different branches of the intestinal vasculature. Sporadic cases of splenic infarction and acute pancreatitis were reported. Box 3 summarizes the major abdominal manifestations associated with APS, classified according to the involved organs⁽²⁸⁾. Thrombosis of the hepatic veins as a manifestation of APS results in Budd-Chiari syndrome. Mesenteric and portal venous thrombosis in APS are well described. Other manifestations of large- and small-vessel thrombosis include hepatic infarction, pancreatitis, esophageal necrosis, intestinal ischemia and infarction, colonic ulceration, acalculous cholecystitis with gallbladder necrosis, and giant gastric ulceration⁽⁴⁾.

Box 3 : Summary of the abdominal manifestations associated with the antiphospholipid syndrome

Abdominal Organ	Manifestations
Liver	Budd-Chiari Syndrome: Hepatic-veno-occlusive disease and occlusion of small hepatic veins Nodular regenerative hyperplasia Hepatic infarction Cirrhosis Portal hypertension Autoimmune hepatitis Biliary cirrhosis Liver transplantation
Intestine	Acute intestinal infarction Intestinal angina Intestinal bleeding High prevalence of aPL but no increased vascular thromboses in inflammatory bowel disease
Spleen	Splenic infarction Autosplenectomy or functional asplenia.
Pancreas	Acute pancreatitis

Renal

The revised criteria committee recommends the term aPL-associated nephropathy (APLN) for the renal manifestations of APS. Thrombosis can occur at any location within the renal vasculature. Clinical spectrum includes renal artery stenosis and/or malignant hypertension, renal infarction, renal vein thrombosis, thrombotic microangiopathy, increased allograft vascular thrombosis, and reduced survival of renal allografts. More recently non-thrombotic conditions like glomerulonephritis have also been reported. Thus, the kidney appears to be a major target organ in both primary and secondary APS. Early detection of renal involvement may improve the prognosis of these patients⁽²⁹⁾.

Endocrine

Adrenal insufficiency is the most common endocrine manifestation and can be the presenting symptom of APS. Clinicians should have a high index of suspicion for adrenal insufficiency in patients with APS. Circulating aPL have been detected in some cases of autoimmune thyroid disease, hypopituitarism (including a case of Sheehan's syndrome), diabetes mellitus and rarely ovarian and testicular disease.

Retinal Disorders

Venous and arterial thrombosis of the retinal vasculature is a well-recognized manifestation of APS. Presentation strongly suggestive of the presence of aPL includes the diffuse occlusion of retinal arteries, veins, or both, and neovascularization at the time of presentation. Other ophthalmic manifestations included optic neuropathy and cilioretinal artery occlusion.

Hematologic Disorders

Thrombocytopenia (platelet count <100,000)⁽⁵⁾ is present in from 20% to 40% of patients with APS and is usually mild. Severe thrombocytopenia is most often seen in patients with CAPS and those with concomitant disseminated intravascular anticoagulation or TTP. To clarify the significance of thrombocytopenia in patients with aPL, patients are designated as having aPL-associated thrombocytopenia if there is coexistence of aPL laboratory criteria with thrombocytopenia (platelet count <100,000) confirmed at least twice, 12 weeks apart and exclusion of patients with TTP, disseminated intravascular coagulation, pseudothrombocytopenia, or heparin-induced thrombocytopenia⁽⁷⁾.

Catastrophic Antiphospholipid Syndrome (CAPS)

CAPS, a syndrome of multisystem involvement as a manifestation of APS, was first described by Asherson⁽³⁰⁾ and is also known as Asherson's syndrome. Occurring in fewer than 1% of APS patients, the syndrome is characterized by multiple small-vessel occlusions leading to multiple organ failure and substantial morbidity and mortality⁽³¹⁾. The syndrome is generally of acute onset and defined by the involvement of at least three different organ systems over a period of days or weeks. Histopathologically, there is evidence of small- and large-vessel occlusions. The striking feature of the syndrome is the presence of an acute microangiopathy, rather than the large-vessel occlusions more typically observed in patients with both primary and secondary APS. Clinical features are the manifestations of organ and tissue ischemia and include renal failure due to renal thrombotic microangiopathy, acute respiratory failure due to adult respiratory distress syndrome, cerebral injury due to microthrombi and microinfarctions, and myocardial failure due to microthrombi^(31,32).

Although < 1% of patients with the APS develop the catastrophic variant, its potentially lethal outcome emphasizes its importance in clinical medicine today. It develops rapidly following an identifiable triggering factor. Trigger factors include infection, trauma, neoplasia, anticoagulation withdrawal, during pregnancy or puerperium, surgery, and lupus “flares”. Criteria for diagnosis include the involvement of three or more organs, systems, and/or tissues (Box 4)⁽³²⁾

Box 4 : Preliminary criteria for the classification of CAPS^a

1. Evidence of involvement of 3 organs, systems, and/or tissues^b.
2. Development of manifestations simultaneously or in <1 week
3. Confirmation by histopathology of small-vessel occlusion in at least one organ/tissue^c.
4. Laboratory confirmation of the presence of aPL (lupus anticoagulant and/or aCL an/or anti β 2 GP I)

Definite CAPS

All four criteria

Probable CAPS

- Criteria 2, 3, and 4, plus evidence of involvement of only two organs, systems, and/or tissues
- All four criteria, except for the absence of laboratory confirmation of the presence of aPL at least 6 weeks after a first positive result (because of the early death of a patient never tested for aPL before onset of CAPS)
- Criteria 1,2, and 4
- Criteria 1,3, and 4, plus the development of a third event in >1 week but <1 month, despite anticoagulation treatment

^aProposed and accepted during the 10th International Congress on Antiphospholipid Antibodies (aPL), September 2002.

^bUsually clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate.

Renal involvement is defined by a 50% rise in serum creatinine, severe systemic hypertension (>180/100 mm Hg), and/or proteinuria (>500 mg/24h).

^cFor histopathologic confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.

The mortality in CAPS is high, although with early and effective treatment an improvement in this high death rate has been noted recently⁽³³⁾. High index of clinical suspicion and careful investigation are required to make early diagnosis and initiate prompt treatment. Cerebral involvement, mainly consisting of stroke, followed by cardiac involvement and infections are considered as the main causes of death in patients with CAPS. The presence of SLE is also related with higher mortality⁽³⁴⁾.

Few other entities

Asymptomatic Antiphospholipid Antibodies

As the precise genesis of aPL is poorly understood. Why some individuals with no underlying medical disorder develop aPL is also not clear and Why some individuals develop thrombosis and some do not also remains poorly understood. While aPL may be present as a predisposing risk factor, the addition of a triggering risk factor, or "double hit," may be required for the development of thrombosis⁽²⁾. Identifiable risk factors for transition from asymptomatic aPL to APS (aPL with thrombosis) include a prior history of thrombosis, the presence of lupus anticoagulant, and an elevated level of aCL IgG. Various reports suggest that each of these risk factors increase the risk of thrombosis about fivefold. Persistence of aPL over time also progressively increases thrombosis risk. As the line between patients with asymptomatic aPL and those with APS is defined by the development of large- or small-vessel thrombosis, or pregnancy loss, it is important to keep the asymptomatic individuals under careful clinical surveillance for thrombosis.

Probable Antiphospholipid Syndrome

Many patients positive for aPL exhibit clinical features suggesting APS but lack the clinical criteria of vascular thrombosis or pregnancy loss necessary to substantiate a diagnosis of "definite" APS. Such patients have been classified as probable APS or pre-APS. Clinical manifestations include

livedo reticularis, chorea, thrombocytopenia, fetal loss, and cardiac valvular lesions. Some studies have indicated that cutaneous manifestations such as Livedo reticularis are the first manifestation of APS in up to 41% of patients with APS.

Seronegative Antiphospholipid Syndrome (SNAP)

A subset of patients has been identified who exhibit clinical manifestations of APS, without identifiable aPL, lupus anticoagulant, β -2-GP I, antiphospholipid subtype antibodies, or any other recognized aPL on laboratory testing. These individuals are said to have SNAP syndrome⁽³⁶⁾. Such patients develop idiopathic arterial or venous thrombosis and initial testing for aPL is negative. Repeat testing months later may be positive⁽³⁶⁾.

Microangiopathic Antiphospholipid Syndrome

Patients with APS may present with a variety of disorders characteristic of microvascular occlusive disease. Such disorders include thrombotic thrombocytopenic purpura (TTP); hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; thrombotic microangiopathic hemolytic anemia; and Catastrophic antiphospholipid syndrome (Asherson's syndrome). Syndromes may also exhibit overlapping features characteristic of more than one of these conditions. All share the pathologic features of microangiopathy.

Drug-Induced Antiphospholipid Syndrome

A variety of medications have been documented to induce the formation of aPL. These have included chlorpromazine, phenytoin, hydralazine, procainamide, fansidar, quinidine, interferon, and cocaine. A common misconception is that patients who have drug-induced APS, often immunoglobulin (Ig) M, do not suffer thrombosis, but in fact they have an increased risk of thrombosis^(37,38).

Infection-Associated Antiphospholipid Syndrome

A variety of infectious agents trigger the production of aPL⁽³⁹⁾. Autoantibodies are more often IgM than IgG. The clinical features typical of APS are less commonly observed with aPL associated with infections⁽³⁹⁾. Some infections, however, have been well documented to be associated with the development of aPL and β -2-GP I and are thus more likely to be associated with the subsequent development of thrombosis (leprosy, parvovirus B19, HIV, hepatitis C virus, cytomegalovirus)⁽³⁹⁾. Infection may be the triggering factor in as many as 40% of cases of CAPS.

Malignancy-Associated Antiphospholipid Syndrome

A variety of solid and hematologic malignancies have been reported to be associated with the presence of aPL. The relationship between malignancy, the development of aPL, and thrombosis is poorly understood.

Antiphospholipid Syndrome Antibodies

The antibodies that manifest as the APS can target phospholipids directly⁽⁶⁾. These anti-phospholipid antibodies (APAs) target cardiolipin, phosphatidylserine, phosphatidylinositol, phosphatidylethanolamine, phosphatidylglycerol, and phosphatidylcholine. APAs can be IgG, IgA, and IgM idiotypes. APAs are subgrouped based on type of antibody. The presence of APAs may be associated with either venous or arterial thrombosis. APS can also be caused by antibodies that target protein antigens which bind to anionic phospholipids, forming a protein-phospholipid complex. The predominant antibodies in APS are those that target the proteins beta-2-glycoprotein I

(β -GPI) and prothrombin, although other antigenic targets have been identified in APS patients. For example, antibodies against annexin V and protein C have been shown to be associated with APS and SLE.

The term LA is based on a laboratory artifact. Because this antibody interferes with the action of phospholipid cofactors in the coagulation cascade in laboratory assays, a prolongation of the time to clot is produced, mimicking an apparent anticoagulant response. This is a misnomer, because the presence of an LA is associated with clinical thrombosis and not bleeding. Specifically, the LA inhibits the formation of the prothrombinase complex within the coagulation cascade. It blocks the binding of prothrombin and factor Xa to phospholipids, which inhibits the conversion of prothrombin to thrombin and clot formation. The LA can be an IgG, IgA, or IgM. The LA is found in at least 10% of patients who have SLE and in many patients who have autoimmune disorders. LA is commonly associated with venous thrombosis and only occasionally with arterial disease.

Detection of Subtypes of Antiphospholipid Antibodies

When patients experiencing thrombosis or recurrent miscarriage are suspected of harboring APAs and assays for ACAs or LACs are negative, the clinician should suspect discordant subgroups and order assays for anti- β 2-Gpl and antibodies to phosphatidylserine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, annexin-V, and phosphatidylcholine. These assays are all available by enzyme immunoassay and must be tested for in the appropriate clinical situations.

Management

Pregnancy losses, either recurrent early miscarriage or fetal death, are among the most characteristic clinical manifestations of APS. Historically, prednisone, aspirin, heparin and immunoglobulins have all been used in the treatment of pregnancy losses in women with APS. Prednisone, usually in combination with aspirin, was initially used for the obstetric manifestations of APS. However, a case series and two small, randomized clinical trials showed that the use of corticosteroids represented no benefit over regimes containing aspirin \pm heparin in pregnant women with APS, actually increasing the rate of complications such as prematurity and hypertension. Likewise, immunoglobulins have not demonstrated superiority against heparin and aspirin in two small RCTs^(40,41). Thus, prednisone and immunoglobulins are not among the first line drugs for treating miscarriage in women with APS.

According to a recent review by Petri and Qazi⁽⁴²⁾, the final recommendation for women with APS and one fetal loss or multiple first trimester losses is aspirin plus heparin, either unfractionated heparin (UFH) or low molecular weight heparin (LMWH). However, Pauzner et al⁽⁴³⁾ observed no significant differences in pregnancy outcomes when a group receiving enoxaparin was compared to other group receiving warfarin. No serious fetal or maternal bleeding was seen in either group. Thus, warfarin can be used in selected patients during pregnancy, but only after organogenesis (weeks 6–12) is complete, due to the high risk of fetal malformations. The INR must be closely controlled to minimize the probabilities of serious fetal bleeding. Nursing is safe during warfarin and heparin therapy⁽⁴⁴⁾.

New research on the role of complement activation in murine APS pregnancy loss may change therapeutic options in the future⁽⁴²⁾. Thus there has not been a final word on the subject yet.

Current Recommendations (Box 5)

Primary thrombosis prevention (prevention of a first clot) in individuals who are persistently aPL-positive lacks an evidence-based approach; controlled, prospective, and randomized studies are in progress^(45,46). For secondary thrombosis prevention (prevention of a second clot), the current recommendation is life-long warfarin, although the necessity, duration, and intensity of warfarin treatment are still under debate. Strategies for the prevention of fetal loss in patients who have a prior history of fetal loss include low-dose aspirin and low molecular weight heparin (LMWH) for patients fulfilling the Sapporo APS Criteria. If patients fail this regimen, a common next step is the addition of intravenous immunoglobulin (IVIG), shown to be efficacious in case reports only (see Box 5)⁽⁴⁷⁾. For CAPS, the highest survival rate is achieved with the combination of anticoagulation, corticosteroids, and IVIG or plasma exchange⁽³²⁾. Elimination of reversible thrombosis risk factors (such as smoking or oral contraceptives) and prophylaxis during high-risk periods (such as surgical interventions or prolonged immobilization) are crucial for primary and secondary thrombosis prophylaxis in APS.

Box 5 : Currently recommended treatments for antiphospholipid syndrome	
Clinical Manifestations	Treatment for thrombosis prevention
Vascular Events	
Asymptomatic ^a aPL- positive patients	No treatment ^b
Venous thrombosis	Warfarin (INR: 2.0–3.0)
Arterial thrombosis	Warfarin (INR: 3.0) ^c
Recurrent thrombosis	Warfarin (INR: 3.0–4.0) + low-dose aspirin (LDA)
Catastrophic APS	Anticoagulation + corticosteroids + IVIG or plasmapheresis
Pregnancy morbidity	
Asymptomatic ^a aPL-positive patients	No treatment ^d
Single pregnancy loss <10 wk	No treatment ^d
Recurrent (pre-) embryonic losses ^e or fetal loss > 10 wk and no history of vascular thrombosis	LDA + prophylactic ^f dose heparin during the pregnancy, heparin for postpartum 6–12 w, and LDA thereafter
Recurrent (pre-)embryonic losses or fetal loss >10 w and history of vascular thrombosis	LDA + therapeutic ^f dose heparin during the pregnancy, warfarin postpartum
History of vascular thrombosis	LDA + therapeutic ^f dose heparin during the pregnancy, warfarin postpartum

a No history of thrombosis or pregnancy morbidity.
b LDA (81 mg/d) or hydroxychloroquine may be given.
c The intensity of anticoagulation is controversial.
d Although no data support the use of LDA in this situation, it is commonly given because of low risk of adverse events.
e <10 wk of gestation.
f Prophylactic dose such as enoxaparin 30–40 mg subcutaneously once daily and therapeutic dose such as enoxaparin 1 mg/kg subcutaneously twice daily or 1.5 mg/kg subcutaneously once daily.

How much warfarin should be used?

High-intensity warfarin had been the recommendation for secondary thromboprophylaxis in APS patients for the last decade. However, two recent prospective randomized

controlled trials with two intensities of warfarin concluded that both moderate (INR 2–3) and high intensity anticoagulation (INR 3–4) are similarly protective in APS patients after the first thrombosis^(48,49). When the results of the two studies were combined in a meta-analysis, a significant excess of minor bleeding was evident in patients allocated to high intensity warfarin. Thus, it would be desirable to treat patients with APS with usual-intensity warfarin with a target INR of 2.5. A higher INR can be considered if recurrence occurs on this INR. It is possible that the current “antithrombotic” approach to patients with APS will be replaced by a “more specifically targeted, anti-inflammatory or immunomodulatory” approach in the future⁽⁵⁰⁾. The intensity of the anticoagulation is still a matter of debate for APS patients with arterial events since in both studies patients with arterial events constituted less than half of the study population.

Currently, there is no data to support the primary prevention of stroke in asymptomatic carriers of aPL. In patients with other vascular risk factors, the use of low dose aspirin is reasonable. Such patients should also have vigorous counseling regarding the importance of reducing modifiable vascular risk factors. Current practice is to anticoagulate patients with aPL suffering from cerebral ischaemia with a target INR of 3.0 to prevent recurrences. Low-dose aspirin alone does not seem helpful to prevent recurrent thrombosis in these patients. Thus, once the patient has had a proven thrombosis associated with aPL, long-term (possibly life-long) warfarin therapy is advisable. Oral anticoagulation carries a risk of haemorrhage, but the risk of serious bleeding in patients with APS and previous thrombosis treated with oral anticoagulation to a target INR of 3.5 is similar to that in groups of patients treated with lower target ratios.

For how long should warfarin be used?

Conventional wisdom supported by several retrospective anecdotes states that warfarin treatment should be lifelong. Studies in non-APS patients with thrombosis cite venous recurrence risk at 10% per year on stopping the treatment after 3, 6, 12, or 24 months. The best available evidence from subgroup studies of these populations suggests that the recurrence risk may not be higher in patients with aPL. Furthermore, most studies of recurrence rate do not take other risk factors into account. Some patients eventually lose aPL positivity; others spend years with no recurrence after a ‘triggered’ thrombosis, the trigger being trauma including surgery, oestrogen therapy, etc. Many investigators are now asking whether it might be possible to withdraw anticoagulation if trigger factors are no longer present. Studies addressing this question are just beginning.

Is warfarin a complete treatment for APS?

Although warfarin is the drug of choice for the treatment of thromboembolism, it may be inappropriate for many APS related conditions. Specifically, no data indicate the efficacy of warfarin in the treatment of microangiopathic nephropathy, valvular heart disease, livedo reticularis, or leg ulcers. Also, no data support its use in asymptomatic bearers of aPL. In a recent prospective cohort study, 178 persistently aPL-positive but thrombosis-free individuals were followed for 3 years without prophylactic treatment (except during high-risk periods) and no patients developed thrombosis during the study period⁽⁵¹⁾.

Are there alternatives to warfarin?

Antiplatelet agents such as dipyridamole, aspirin with dipyridamole, ticlopidine, or clopidogrel bisulfate have been used for secondary prevention after non-cardioembolic strokes or TIAs; but except for clopidogrel, the others have not been formally tested in APS. Recurrence rates/100 patient years of 5–10% have been documented with agents like aspirin, clopidogrel and LMWH, which are not too different from those observed with warfarin. The use of these alternative agents (Box 6) can be considered for those patients who cannot be given warfarin. Intravenous direct thrombin inhibitors in clinical use are lepirudin, argatroban, and bivalirudin. No data on use of these agents in aPL-positive patients exist; these agents, however, are used in APS patients in the presence of heparin induced thrombocytopenia.

A few case reports have started to appear about patients with APS and CAPS, resistant to conventional medications, who responded to treatment with rituximab, an anti-CD20 monoclonal antibody. No formal trials have yet been reported.

Although there is experimental and clinical evidence that hydroxychloroquine may play a role in the management of aPL-positive patients, controlled studies are needed to determine the effectiveness of hydroxychloroquine for primary and secondary thrombosis prevention in APS. Statins have anti-inflammatory effects including decreasing the expression of adhesion molecules in monocytes, interfering with leukocyte–endothelial interaction, inhibiting platelet function, and downregulation of inflammatory cytokines in endothelial cells. In aPL-treated mice, fluvastatin diminishes thrombus size, an effect independent of the cholesterol-lowering effects of statins. Although statins have been used in primary and secondary cardiovascular disease prevention, no data exist in aPL-positive patients for thrombosis prevention. In the presence of experimental evidence, the role of statins in both primary and secondary thrombosis prevention in aPL-positive patients should be investigated.

Ximelagatran is the first oral thrombin inhibitor, which neutralizes clot-bound thrombin. The active metabolite of ximelagatran is melagatran, which has a wider therapeutic window, rapid onset of action, and shorter half-life than warfarin. Furthermore, ximelagatran does not have any known interaction with drugs or food. Ximelagatran is superior to warfarin in the prevention of venous thromboembolism after total knee replacement surgery⁽⁵²⁾, as effective as enoxaparin followed by warfarin for the initial treatment of venous thromboembolism⁽⁵³⁾, and superior to placebo for the extended (6–18 months after warfarin treatment) prevention of venous thromboembolism⁽⁵⁴⁾. As ximelagatran causes transient liver function elevations in about 6% of patients, the Food and Drug Administration voted against its approval in September 2004⁽⁵⁵⁾.

Box 6: Alternatives to Warfarin

Current	Future
Nonaspirin antiplatelet agents	GPIIb/IIIa-specific antagonists
Indirect and direct thrombin inhibitors	p38MAPK inhibitors
Hydroxychloroquine	Thromboxane A2 inhibitors
Statins	Tissue factor expression inhibition
Rituximab	Complement inhibition
Recombinant human activated protein C	Synthetic peptides
Prostacyclin and prostaglandin	bGPI toleragen
Anticytokine treatment	New anticoagulants in development

Autologous Hematopoietic Stem Cell Transplantation (HSCT)

Good results have been reported with autologous hematopoietic stem cell transplantation (HSCT) in APS. Statkute et al.⁽⁵⁶⁾ reported 19 persistently LAC or aCL-positive (> 40 IU/ml) lupus patients (11 with definite APS fulfilling the Sapporo classification criteria) who received HSCT for active lupus. Six of eight LAC-positive, five of seven aCL IgG-positive, and nine of eleven aCL IgM-positive patients became and remained negative (median follow-up 24 months) following the transplantation. Anticoagulation was stopped in 9 of 10 definite APS patients who were on warfarin before the transplantation (median time to stop warfarin 5 months) and 3 of 9 patients had thrombosis recurrence after a median follow-up of 7 months.

It is highly possible that the current antithrombotic approach to patients who are aPL-positive will be replaced by a more specifically targeted, anti-inflammatory or immunomodulatory approach in the future.

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