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Antiphospholipid syndrome

Zeinab A. El-Sayed
Professor of Pediatrics, Ain Shams University.

Definition: Antiphospholipid syndrome (APS) (Hughes syndrome) is a disorder characterized by recurrent venous or arterial thrombosis and/or fetal losses associated with typical laboratory abnormalities.

Frequency: Actual frequency in the general population is unknown. Antiphospholipid (aPL) antibodies can be found in 1-5% of the healthy population. Anticardiolipin (aCL) antibody tends to occur more frequently in elderly individuals. Recent literature suggests that the occurrence rate of APS in patients with SLE is 34-42%. Antiphospholipid antibody-related thrombosis seems to constitute a significant proportion of childhood thromboses. About one third of children suffering a thrombotic event have circulating antiphospholipid antibodies, and more than two thirds of children with idiopathic cerebral ischemia meet the criteria for the diagnosis of antiphospholipid antibody syndrome

Sex: A female predominance is documented, particularly for secondary APS. This parallels the association of APS with SLE and other connective-tissue diseases, which also have a female predominance.

Age: APS occurs more commonly in young-to-middle–aged adults; however, it also manifests in children and elderly people. Disease onset has been reported in children as young as 8 months.

Pathophysiology: An alteration of the homeostatic regulation of blood coagulation occurs; however, the mechanisms of thrombosis are not yet defined. Although aPL antibodies are clinically linked to APS, whether they are involved in the pathogenesis or are an epiphenomenon is unclear.

One hypothesis postulates a defect in cellular apoptosis, which exposes membrane phospholipids to the binding of various coagulation proteins. Once bound, a phospholipid-protein complex is formed and a neoepitope is uncovered, which subsequently induces and becomes the target of autoantibodies. These antibodies are directed against phospholipid-binding proteins expressed on, or bound to, the surface of vascular endothelial cells or platelets. The main protein associated with aCL antibody activity is ß2-glycoprotein I (ß2GPI) bound to phospholipids. ß2GPI is a highly glycosylated single-chain protein that is present in plasma and avidly binds to negatively charged phospholipids such as cardiolipin, phosphatidylserine, or phosphatidylinositol.

Causes: APS is an autoimmune disorder of unknown cause. APS can occur in patients without evidence of any definable associated disease (primary APS). It may also occur in association with SLE or another rheumatic or autoimmune disorder (secondary APS). Clinical conditions in which aPL antibodies are found are listed in table 1.

Table 1: Conditions in which aPL antibodies were reported:

- Autoimmune or rheumatic diseases such as:
  - SLE
  - Sjögren syndrome
  - Rheumatoid arthritis
  - Autoimmune thrombocytopenic purpura
  - Autoimmune hemolytic anemia
  - Mixed connective-tissue disease
  - Polymyalgia rheumatica or giant cell arteritis
  - Behçet syndrome
- Infections
  - Syphilis
  - Hepatitis C
  - HIV infection
  - Human T-cell lymphotrophic virus type 1 infection
  - Malaria
  - Bacterial septicemia
- Drugs
  - Cardiac - Procainamide, quinidine, propranolol, hydralazine
  - Neuroleptic or psychiatric - Phenytoin, chlorpromazine
  - Other - Interferon alpha, quinine, amoxicillin
- Liver disease, chronic renal failure, sickle cell disease.
- Relatives of persons with known APS.

Diagnosis:

The American College of Rheumatology has proposed clinical classification criteria for APS in adults. Preliminary criteria were also set for children (Table 2).

Table 2. Preliminary criteria for the classification of pediatric antiphospholipid syndrome.

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.
Laboratory criteria:	1. Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma Must be present in medium or high titer (i.e. >40 GPL or MPL, or >99th percentile) on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay. 2. Anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma Must be present in titer >99th percentile, on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay. 3. Lupus anticoagulant in plasma Must be present on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and hemostasis
Pediatric APS is considered to be present if the clinical criterion and at least 1 of the laboratory criteria are met.	

The following clinical features also may be attributable to APS:

- Neurologic symptoms, such as migraine, chorea, seizures, transverse myelitis, Guillain-Barré syndrome, or dementia (rare)
- History of heart murmur (mitral or aortic regurge) or cardiac valvular aseptic vegetations especially in patients with autoimmune diseases
- Hematologic abnormalities, such as thrombocytopenia or hemolytic anemia
- Livedo reticularis (figure 1), necrotic skin ulcers.
- Unexplained adrenal insufficiency
- Avascular necrosis of bone in the absence of other risk factors
- Pulmonary hypertension
- Ascites (Budd-Chiari syndrome)
- Hepatomegaly
- Nephrotic syndrome due to thrombotic microangiopathy

The Catastrophic APS: (Table 3)

This is an acute devastating syndrome characterized by multiple vascular occlusions which often results in death. A catastrophic APS occurs in 0.8% of the patients.

Other antiphospholipid antibodies: There are other antiphospholipid antibodies that are currently not included in the laboratory criteria. These include: anticardiolipin IgA antibodies, and antiphospholipid antibodies directed against phospholipids other than cardiolipin (e.g., phosphatidylserine and phosphatidyl-ethanolamine) or against phospholipid-binding proteins other than cardiolipin-bound β2-glycoprotein I (e.g., prothrombin, annexin V, protein C, or protein S).

Recent literature suggests that an abnormal LA finding is the laboratory test result that confers the strongest risk for thrombosis.

Table 3. Preliminary criteria for the classification of catastrophic APS

1. Evidence of involvement of three or more organs, systems, and/or tissues*
2. Development of manifestations simultaneously or in less than 1 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 (lupus anticoagulant and/or anticardiolipin antibodies)***

* Usually, 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/24 hours). ** For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally. *** If the patient had not been previously diagnosed having an APS, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS.

Differential Diagnosis

Other diseases (e.g., malignancy, nephrotic syndrome, polycythemia, or thrombocytosis), including congenital prothrombotic states, should be considered in the differential diagnosis of APS. Antiphospholipid syndrome can present with arterial or venous thrombosis as can homocystinemia and prothrombin 20210

mutation, whereas patients with protein C, protein S, antithrombin III deficiency, and factor V Leiden usually present only with venous thrombosis.

Treatment

APS patients with vascular events

Long-term anticoagulation with warfarin is the standard of care to prevent a recurrent vascular event in APS patients. The recurrence rate in untreated patients is 44% to 55% following the first vascular event, and approaches 0% in patients treated with high intensity warfarin.

Anticoagulation is initiated in a standard manner with heparin (either intravenous or subcutaneous low-molecular-weight heparin [LMWH]). For those patients with elevated baseline aPTT or who are on LMWH, monitoring to assure adequate anticoagulation can be accomplished by measuring peak and trough activated factor X levels. Initial heparin treatment is followed by long-term warfarin, usually at high intensity (INR>3). There are recent studies suggesting that lower levels might be effective in preventing venous thromboembolism. Thus, some prefer to advocate an INR of 2.0 to 3.0 for those with first venous thrombosis, reserving intensive anticoagulation (INR 3.0 to 4.0) for those with recurrent venous thrombosis or arterial thrombosis. Low-dose aspirin can be added to warfarin if there are ongoing signs of ischemia even if this combination therapy increases the risk of bleeding complications.

Duration of therapy: Normalization of the LAC or aCL is not an indication to discontinue anticoagulation, because patients remain at risk for new thrombosis regardless of change in titer. There is high risk of recurrent thrombosis especially in the 6 months following discontinuation of warfarin. Thus, APS patients with vascular events should be kept on warfarin indefinitely.

In children: Warfarin therapy in children is age and weight dependent. Long term high intensity warfarin therapy may raise concerns of hemorrhage during play and sports. Thus, heparin is given followed by warfarin to keep the INR at 2.5, followed by long term warfarin to maintain an INR at 1.5 to 2.

APS patients with minor manifestations

Platelet counts greater than 50 x 10^9/L due to APS require no specific therapy. Corticosteroids and/or intravenous immunoglobulin (IVIG) are the first line treatments for lower platelet counts. Platelet transfusions are usually not helpful in APS patients as the mechanism of thrombocytopenia is thought to be destructive, and in addition, they may increase the risk of thrombosis. IVIG, danazol or even splenectomy may be considered in corticosteroid-resistant cases.

Catastrophic APS patients

The highest survival rate is achieved with the combination of anticoagulation, corticosteroids, and plasma exchange or intravenous gammaglobulins. Plasma exchange with fresh frozen plasma should be especially indicated if features of microangiopathic hemolytic anemia (i.e., schistocytes) appear.

Asymptomatic aPL-positive patients

Asymptomatic aPL-positive patients generally receive no treatment until after they have a thrombotic event. However, recent reports emphasize the prophylactic role of aspirin.

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