

Update on Antiphospholipid Syndrome (APS)

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OVERVIEW

APS is an acquired prothrombotic state associated with antiphospholipid antibodies namely anticardiolipin antibody (ACLA), lupus anticoagulant (LA) or anti-beta 2 glycoprotein 1 antibody (AB2GP1 Ab). Antiphospholipid antibodies (APLA) are directed against phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl glycerol etc. Anticardiolipin antibody is directed against diphosphatidyl glycerol. Active antigen for LA is still not identified and even though it is an anticoagulant *in vitro* tests, it is actually a procoagulant *in vivo* and probably acts via many procoagulant mechanisms proposed for APS.

APS can be primary or secondary to SLE, other connective tissue diseases, autoimmune hypothyroidism, malignancies, infections like Human Immunodeficiency Virus (HIV) and drugs. A search for associated illnesses mentioned above are needed. Common clinical clues are cerebrovascular accident, myocardial infarction, pulmonary thromboembolism, deep vein thrombosis, recurrent fetal loss without known risk factor, nonhealing ulcer, livedoreticularis etc. Anticardiolipin antibody is detected by ELISA test using fetal calf serum as a source of β_2 GP1 to pick up pathogenic ACLA; Lupus anticoagulant by dilute Russel Viper venom time as the best test. It is believed that the ACLA and LA may be at times negative during a thromboembolic event due to consumption and hence it should be repeated in future follow-up. A subset of seronegative APS described in literature may very well be fitting in this group. ACLA can cause more arterial thrombosis than venous ones and the *vice versa* is for LA. ACLA is 6 times more common than LA in APS and its presence is associated with more than 60 times higher risk of thromboembolism

than that of ACLA negative individuals. As it is believed by most that anticoagulation for this condition should target an INR between 3 and 4 in contrast to all other procoagulant states. Hydroxychloroquine is also recommended in the dose ranging 200 to 400 mg per day in APS. Those with just ACLA or LA positivity without any clinical manifestation can be managed with antiplatelet agents, although it is not fully established as evidence to prevent thromboembolism. Role of steroid comes mainly in lifethreatening catastrophic APS, although some argue now that immunosuppression may be used in APS in general. Treatment of pregnancy loss involves heparin with or without low dose aspirin. Use of intravenous immunoglobulin (IVIg) in refractory cases has also been reported.

HISTORY

During Second World War, 'biological false positive test for syphilis (BFPSTS)' created a new enigma to medical science. And it remained so till Harris in 1984 standardised the assay for anticardiolipin antibody when the concept of APS or Hughe syndrome was born. Since then several diseases were explained by this mechanism and treatment became possible including that for those earlier known as "lupus like illnesses or probable Systemic Lupus Erythematosus (SLE)." APS can be a great mimic like lupus with varied manifestations depending on the system involved. In fact, one-third of primary APS may evolve into SLE during follow-ups.

DEFINITION

APS is an acquired prothrombotic state characterized by presence of one or more of the APLAs mainly anticardiolipin antibody (ACLA) or lupus anticoagulant (LA)

plus one of the clinical manifestations namely arterial thrombosis, venous thrombosis and recurrent fetal loss. Thrombocytopenia and autoimmune hemolytic anemia are also strong clinical associations.

PREVALENCE

Pooled data show that APS is the commonest acquired prothrombotic state, just like factor V Leiden mutation is the commonest cause of congenital prothrombotic state. Its exact prevalence is still not clear as more and more of ischemic and prothrombotic illnesses are being described due to APS and the process continues. One earlier population data from Kuwait calculated the incidence of 52 patients/million population/year based on a hospital based data of 2.66/1000 admissions in medical wards.

Its prevalence in autoimmune connective tissue diseases (secondary APS) is much higher, highest being in SLE. Autoimmune hypothyroidism is also a very common association of APS. Even in rheumatoid arthritis the mean prevalence was calculated at 28% in one study and the median was 22%.² Several studies show that most cases of Budd-Chiari syndrome, migratory thrombophlebitis of malignancy are indeed primary antiphospholipid syndrome.

PATHOGENESIS

How exactly ACLA, LA and beta 2 glycoprotein 1 cause thromboembolism is not fully understood. However, several mechanisms involving endothelium, platelet, activated protein C, antithrombin 3 have been proposed.

Recent studies show that antiphospholipid antibodies (APLA) can stimulate tissue factor (TF) expression by endothelial cells (ECs) and monocytes.³

There are suggestions that APS play several key roles in the innate immune response, and probably become pathologic in susceptible people under adverse intravascular conditions. Some suggest that APLA develop from natural auto-antibodies for host defense⁴.

In APLA-positive patients, there is high levels of beta-thrombomodulin, and microvesicle formation which suggest presence of activated platelets capable of causing thrombosis by persistent exposure of a procoagulant surface⁵.

CLINICAL FEATURES

APLA can cause thromboembolic process anywhere, therefore its manifestation depends on the organ involved.

Here are some of the presentations involving major systems.

Central Nervous System (CNS)

Younger patients presenting with stroke without identifiable risk factors for atherosclerosis, are more likely to have an underlying antiphospholipid syndrome (APLS) as the etiology, and should be screened for it. One Indian study showed 18.18% of such patients with APS.⁶

Although APS frequently present with strokes and TIA, neurologic features include non-thrombotic neurologic syndromes like focal neurologic manifestations.

Testing for APLA in young individuals under the age of 40 with multiple hyperintensity lesions on brain MRI in the absence of other possible causes is now strongly recommended⁷.

Even though Sydney antiphospholipid meet criteria mentions only stroke and transient ischemic attacks, seizures have been repeatedly reported in APS patients⁸.

Renal

All renal vasculatures can be affected causing severe hypertension, proteinuria, hematuria, nephrotic syndrome, ESRD and renal failure. APS patients are at high risk of post-transplant renal thrombosis⁹.

Others report renal artery stenosis and/or malignant hypertension, renal infarction, renal vein thrombosis, thrombotic microangiopathy, reduced survival of renal allografts due to renal allograft thrombosis and even nonthrombotic conditions like glomerulonephritis have also been reported¹⁰.

Cardiac

Cardiac manifestations in APS include most commonly valve thickening and vegetations, premature and accelerated atherosclerosis and myocardial infarction, intracardiac emboli, ventricular dysfunction, and pulmonary hypertension¹¹.

Pulmonary

Pulmonary manifestations in antiphospholipid syndrome (APS) are relatively rare, but can be severe and life threatening often called as "antiphospholipid lung syndrome" characterized by pulmonary microthrombosis, thromboembolism of lung arteries, pulmonary hypertension, adult respiratory distress syndrome, intra-alveolar hemorrhages, postpartum syndrome¹².

Skin

Most common skin manifestation include livedo reticularis, followed by ulcerations, digital gangrene, subungual splinter hemorrhages, superficial venous thrombosis, thrombocytopenic purpura, pseudovasculitic manifestations, extensive cutaneous necrosis and primary anetoderma in the decreasing order of occurrence. Catastrophic antiphospholipid syndrome has higher incidence of skin lesions reflecting generalized vasculopathy¹³.

ENT

Rare manifestations include autoimmune sensorineural hearing loss (ASNHL), a clinical syndrome that typically produces a bilateral rapidly progressive hearing loss. Several autoimmune mechanisms have been implicated, but at least a few of them are due to antiphospholipid antibodies as per literature presenting as sudden/progressive hearing loss¹⁴.

Malignancy Association

Malignancies are often associated with APS. In a series of 120 patients with APS, 10 (8%) patients suffered from B-cell lymphoma, 8 (7%) from spleen lymphoma, 7 (6%) from chronic myeloid leukemia, and 6 (5%) from non-Hodgkin's lymphoma (NHL). Regarding solid tumors, renal cell carcinoma was diagnosed in 7 (6%) patients, tumor with unknown origin in 7 (6%), lung adenocarcinoma in 6 (5%), breast carcinoma in 6 (5%), and melanoma in 6 (5%). APS presentations in this group include thrombocytopenia (25%), cerebrovascular accidents (24%), deep vein thrombosis (19%), pulmonary embolism (15%), and heart valve lesions (9%). Catastrophic antiphospholipid syndrome triggered by the malignancy was suspected in 17 cases¹⁵.

Clinical Types

There are attempts to classify APS as below by some:

Type 1–Retinal/CNS/major organs, Type 2–Arterial, Type 3–Venous, Type 4–Arterial and venous, Type 5–Obstetrical, Type 6–Asymptomatic antibody positivity.

Catastrophic APS

Catastrophic APS is a serious form of APS with multiorgan failure with lifethreatening medical emergency and in a series there was 48% mortality in spite intensive care management, primarily attributable to cardiopulmonary failure¹⁶.

Vasculitis and APS

There seem to be a strong association between vasculitis and thrombosis due to APS and the cause effect relationship is not clear; screening for antiphospholipid antibodies in all patients with systemic vasculitis is, therefore, recommended¹⁷.

LABORATORY DIAGNOSIS

Documentation of one of the APLAs is mandatory for diagnosis. Detecting β_2 GPI-1 dependent ACLA is the gold standard for ACLA. LA should be done by DRVVT rather than KCT.

Anti- β_2 GPI assay should not be done as an alternative to ACLA or LA testing.

Although IgG isotype of ACLA is considered more pathogenic, newer evidence suggest even IgM and IgA isotypes are important too¹⁸.

However, in one Indian study with 19 patients of SLE with thrombosis, 14 (73.6%) were positive for anti- β_2 GPI-1 and the authors recommend the test in all cases of SLE to consider prophylactic antithrombotic therapy in these patients¹⁹.

The Sydney update of the classification criteria for definite APS diagnosis introduced numerous changes to preliminary consensus statement. Vascular thrombosis now must be diagnosed objectively and additional risk factors for thrombosis or pregnancy loss must be taken into account before the diagnosis is made.. A single positive test for ACLA, LA and anti- β_2 glycoprotein1 is still sufficient to justify a diagnosis of APS which could overdiagnose this condition. However, multiple or triple positivity could pick up high risk patients for possible recurrence²⁰.

Persistent positivity of APLA, careful exclusion of other prothrombotic states and other causes of fetal loss and repeat testing is required before labeling as 'seronegative APS'²¹.

Diagnosis of catastrophic antiphospholipid syndrome require histopathological evidence of multiple small vessel occlusions in addition to antiphospholipid antibodies, usually in high titre and clinical evidence of multiple organ involvement. This is important as it requires aggressive treatment with high doses of intravenous (IV) heparin, IV steroids, IV gammaglobulins and/or repeated plasma exchanges²².

TREATMENT

Standard and conventional approach to treatment is by anticoagulation to achieve targeted INR between

3 and 4; in addition, hydroxychloroquine is also recommended in the dose ranging from 200 to 400 mg/day. Low dose aspirin is required for those with antibody alone without any clinical event. Recommended treatment for prevention of pregnancy loss in APS requires heparin plus low dose aspirin.

Recent trials suggest some changes. Two randomized trials in patients with antiphospholipid syndrome with initial thromboembolic event now suggest an INR of 2.0 to 3.0 is as good for the prevention of future thrombotic events. With pregnancy, the combination of aspirin and heparin is still the standard of care²³.

More strikingly, one recent systematic review suggests that moderate-intensity warfarin is as effective for preventing recurrent venous thrombosis and perhaps also arterial thrombosis. Even aspirin appears to be as effective as moderate-intensity warfarin for preventing recurrent stroke in patients with prior stroke and a single positive test result for antiphospholipid antibody. Well-designed prospective studies are needed for optimal treatment of other thrombotic aspects of APS²⁴.

With careful monitoring, desensitization may be a safe alternative even during pregnancy in patients with hypersensitivity to aspirin, and aspirin therapy still can continue²⁵.

Although recommendations suggest lifelong anticoagulation for thrombosis in APS, one study showed that abnormal D-dimer test one month after discontinuation of anticoagulation can be used as an indicator for continuation of anticoagulation. In this study, the test was positive in 223 of 608 patients (36.7%) one month after discontinuation of anticoagulation. A total of 18 events occurred among the 120 patients who stopped anticoagulation (15.0%), as compared with three events among the 103 patients who resumed anticoagulation (2.9%), for an adjusted hazard ratio of 4.26 (95% confidence interval [CI], 1.23 to 14.6; $P=0.02$). Thromboembolism recurred in 24 of 385 patients with a normal D-dimer level (6.2%). Among patients who stopped anticoagulation, the adjusted hazard ratio for recurrent thromboembolism among those with an abnormal D-dimer level, as compared with those with a normal D-dimer level, was 2.27 (95% CI, 1.15 to 4.46; $P=0.02$). This study concluded that Patients with an abnormal D-dimer level one month after the discontinuation of anticoagulation have a significant incidence of recurrent venous thromboembolism, which is reduced by the resumption of anticoagulation. The optimal course of anticoagulation in patients with a normal D-dimer level, however, has not been clearly established²⁶.

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