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Review Article

Antiphospholipid syndrome

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Abstract. Antiphospholipid syndrome is characterized by arterial or venous thrombosis and/or recurrent miscarriages together with presence of anticardiolipin antibodies and/or lupus anticoagulant and/or anti-β2-glycoprotein 1 positivity. The exact pathogenic role of antibodies in the development of thrombosis still remains to be fully elucidated. Novel mechanisms involving both the complement pathway and micro-particles have been described. This knowledge might identify novel therapeutic targets and improve the management.

Key words : Antiphospholipid syndrome, Anticardiolipin antibodies, Lupus anticoagulant, anti-β2-glycoprotein 1, Thrombosis, Heparin, Warfarin, Aspirin

1. Introduction

APS is characterized by venous or arterial thrombosis, foetal losses and thrombocytopenia together with documentation of presence of antiphospholipid antibodies (aPL) which include anticardiolipin antibodies (aCL), lupus anticoagulant (LA) and antibodies directed to β2-glycoprotein 1 (β2GP1) (1). Despite the strong association between aPL and thrombosis, the pathogenic role of aPL in the development of thrombosis is not yet fully elucidated.

2. Pathogenetic mechanisms in APS (Fig 1)

The aPL are not directed against phospholipids, but against a wide variety of phospholipids-binding proteins - called cofactors. β2GP1 is the most important antigenic target (2). In fact, only aPL with high affinity for β2GP1 are pathologically relevant.

Infectious agents may be related to the production and clinical manifestations of aPL. aPL may be synthesized by B-cell clones cross reacting with epitopes expressed on infectious agents as the result of molecular mimicry between exogenous molecules and β2GP1 (3). (Fig. 2 and 3).

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Other environmental factors, such as drugs or neoplasms, may also be responsible for inducing aPL. It is possible that auto-antibodies to malignant cells arise secondary to changes in the cell membrane inducing exposure of certain antigens which are normally facing the intracellular compartment (4).

The presence of aPL has also been linked to genetic predisposition i.e. HLA system (5). Variable reports exist regarding association between the Val/Leu247 polymorphism and occurrence of anti-β2GP1 (6,7). Exposure to one or more environmental agents, such as infections, drugs or malignancy, in a genetically predisposed individual, through a molecular mimicry, may result in the production of pathogenic aPL resulting in thrombosis or pregnancy loss.

Another hypothesis explains the existence of natural auto-antibodies that develop for a good purpose but may evolve to become pathogenic under oxidant stress. Antiphospholipid antibodies are detectable in 12% of elderly population and 2% of young population. These auto-antibodies, under oxidant stress, may loose their normal function and lead to autoimmunity.

The clinical manifestations of APS result from the effects of aPL on pathways of coagulation, including the pro-coagulant actions of these antibodies upon protein C, annexin V, platelets and fibrinolysis. In addition to heightening the risk of vascular thrombosis, aPL increase vascular tone and thereby increase the susceptibility to atherosclerosis, foetal loss and neurological damage.

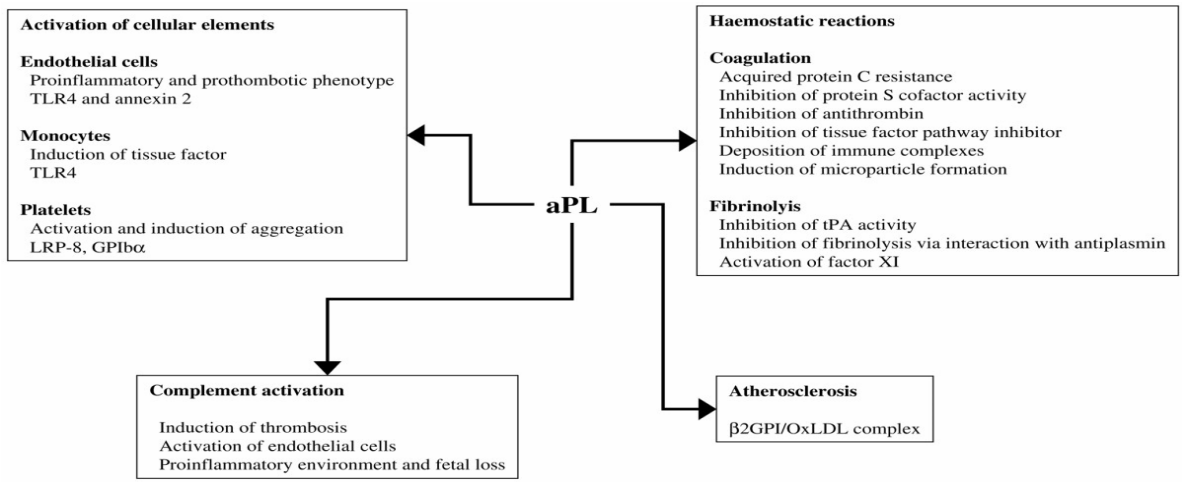

Fig. 1. Current Pathogenetic use of antiphospholipid antibodies. aPL : Antiphospholipid antibodies; β2GP1 / OxLDL : β2 glycoprotein 1 / Oxidized low density lipoprotein; GP1bα : Glycoprotein 1bα; LRP-8 : Low-density lipoprotein receptor-related protein 8; tPA : tissue-type plasminogen activator; TLR4 : Toll-like receptor 4

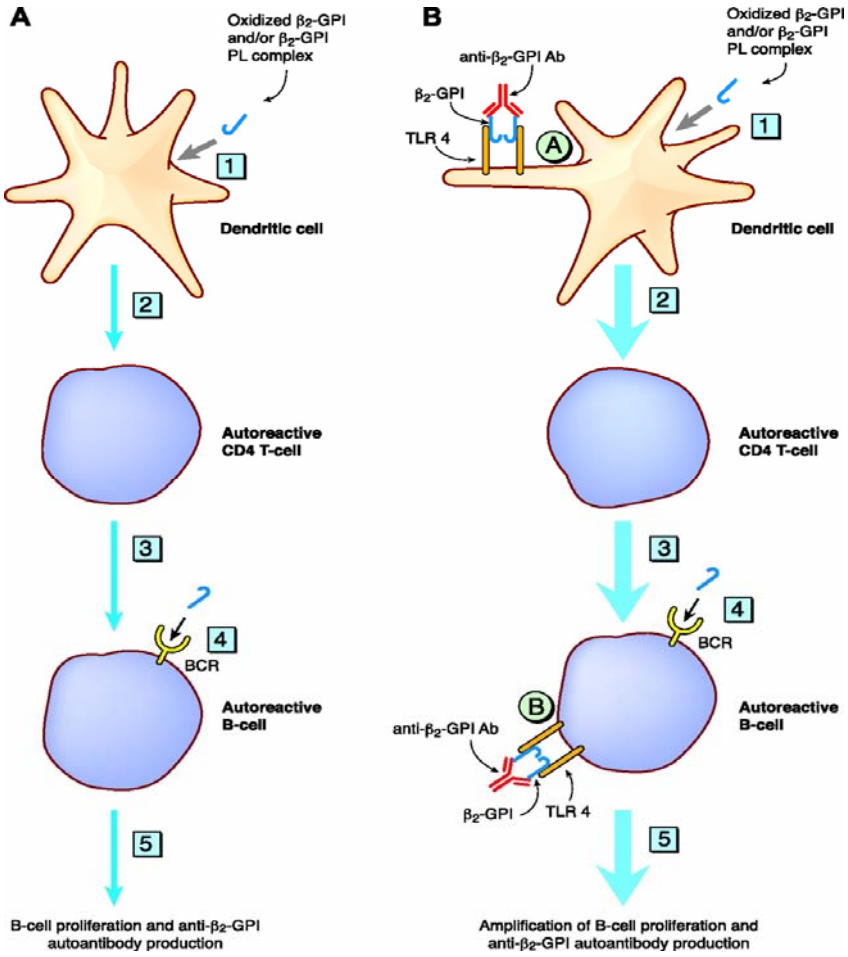

Fig. 2 . Schematic representation of the hypothesis - anti-β2GP1 antibodies in complex with β2GP1 may be able to amplify the production of auto-antibodies via their abilities to bind and cross link Toll-like receptor 4 (with permission from Blood 2007;109:422-430)

Current thinking holds that once aPL are present, a "second-hit" is required for the development of full blown syndrome. Potential candidates for the delivery of such a second-hit include smoking, immobilization, pregnancy, post-partum period, oral contraceptive use, hormone replacement therapy, malignancy etc.

Thrombotic complications correlate more strongly with the presence of LA than positive serologic test.

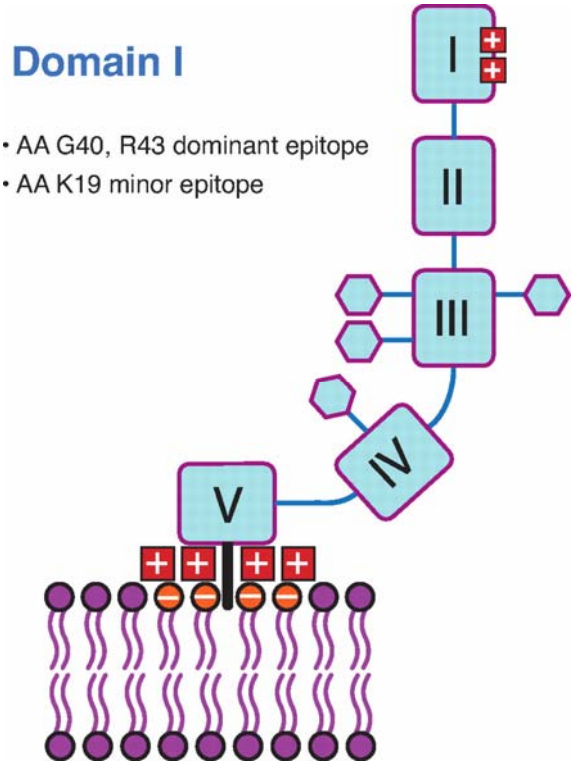

Fig. 3. The β2GP1 B-cell epitope in patients with APS is the domain 1 of the molecule. (with permission from Blood 2009;113:985-994)

3. Clinical manifestations

Clinical spectrum of APS include any combination of occlusive vascular events that may occur in the same individual and the time interval between various events may vary from weeks to years. Deep venous thrombosis affecting legs is the most frequent reported manifestation while cerebrovascular accidents are the commonest arterial thrombotic manifestations. Early and late foetal losses, premature births and pre-eclampsia are the most frequent foetal and obstetric manifestations (2). Various other clinical features such as thrombocytopenia, livedo reticularis and cardiac valvular abnormalities have also been described. Lastly, there are a large variety of unusual clinical manifestations having a prevalence of <5%. These include : large peripheral artery occlusions, chorea, transverse myelopathy, adult respiratory distress syndrome and avascular necrosis of the bone (3).

4. Diagnosis

Laboratory diagnosis of APS requires documentation of aPL which are directed against serum proteins bound to anionic phospholipids. These can be detected by :

- Lupus anticoagulant tests
- Anticardiolipin antibody (ELISA)
- Anti-β2 glycoprotein-1 (ELISA)

Significance of documenting other auto-antibodies e.g. those directed against prothrombin, annexin V, phosphotidylserine and phosphotidyllinositol remains unclear. As APS can occur in the setting of underlying disease such as systemic lupus erythematosus (SLE), tests to document SLE or allied collagen vascular disorders are equally important.

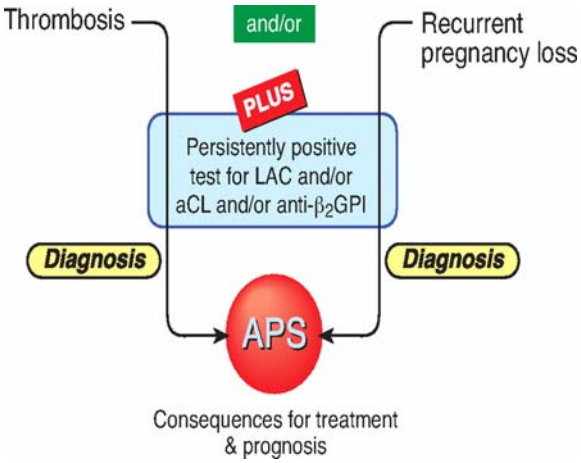

Fig. 4. The updated classification criteria for antiphospholipid syndrome. (with permission from Blood 2009;113:985-994)

5. The Sapporo Classification criteria (Fig 4)

Classification criteria have been proposed during Sapporo and Sydney international consensus conferences. These are useful for research. They may or may not help clinicians as not all of them need to be met to make a clinical diagnosis of APS. These are often referred to as the Sapporo criteria. Definite APS is considered to be present if at least one of the following clinical criteria and at least one of the following laboratory criteria are satisfied.

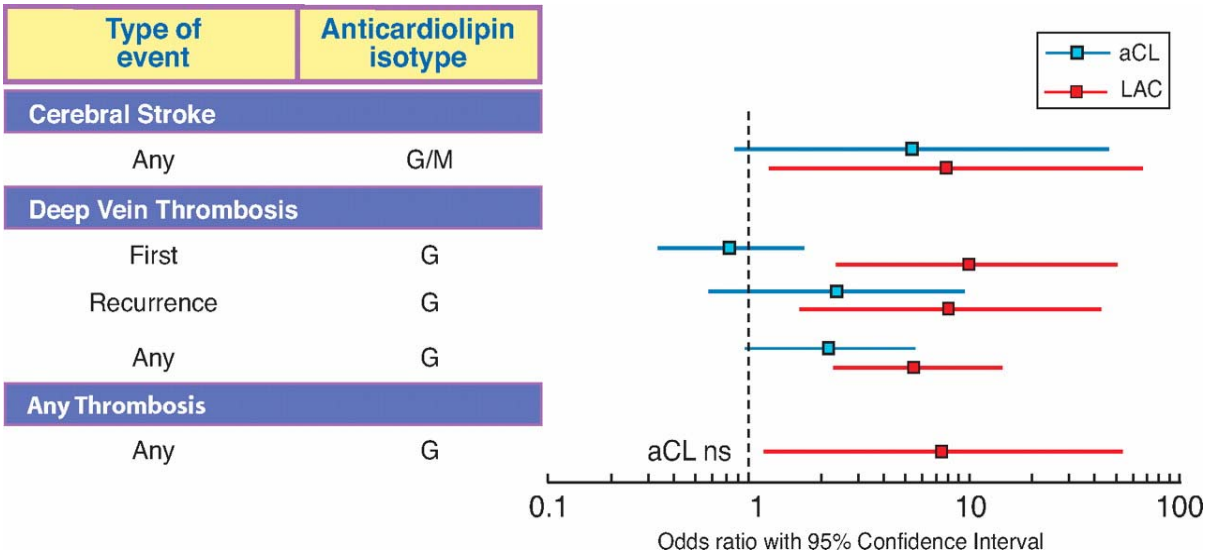

Fig. 5. Lupus anticoagulant correlates better with thrombosis than anticardiolipin antibodies. (with permission from Blood 2009;113:985-994).

6. Clinical criteria

One or more episodes of venous, arterial or small vessel thrombosis and/or morbidity with pregnancy. Thrombosis should be documented by unequivocal imaging or histologic evidence of thrombosis in any tissue or organ. Pregnancy morbidity includes :

- Otherwise unexplained death at ≥ 10 weeks gestation of a morphologically normal fetus
- One or more premature births before 34 weeks of gestation because of eclampsia, pre-eclampsia or placental insufficiency
- Three or more embryonic (<10 week gestation) pregnancy losses unexplained by maternal or paternal chromosomal abnormalities or maternal anatomic or hormonal causes

7. Laboratory criteria

Presence of aPL, on two or more occasions at least 12 weeks apart and no more than 5 years prior to clinical manifestations, as demonstrated by one or more of the following :

- IgG and/or IgM aCL in moderate or high titre (>40 units GPL or MPL or >99th percentile for the testing laboratory)
- Antibodies to β2 glycoprotein-1 of IgG or IgM isotype at a titre >99th percentile for the testing laboratory when tested according to recommended procedures
- Lupus anticoagulant (LA) activity as detected by coagulation based tests such as dilute Russel Viper Venom Time (dRVVT) and Kaolin Clotting Time (KCT)

Lupus anticoagulant correlate better with the thrombotic episodes than the serological tests (Fig 5).

8. Management

Regarding management, there is consensus that patients of APS with first venous thrombosis should be treated with anticoagulation with a target international normalized ratio (INR) of 2.0 to 3.0 (8,9,10). A woman with obstetric manifestations of APS is best treated with aspirin and heparin.[9]

Overall, treatment of both primary and secondary APS is same. It includes :

- Antiplatelet drugs
  a. Aspirin
  b. Clopidogrel
- Anticoagulants
  a. Heparin
  b. Warfarin
- Hydroxychloroquine

9. Antiplatelet drugs

Aspirin is beneficial for primary prophylaxis. It has minimal benefits for the prevention of thrombotic manifestations in patients who have experienced previous events. Clopidogrel may have a role in treatment as well as both primary and secondary prophylaxis, especially in subjects who are allergic to aspirin. There is no advantage of using clopidogrel in place of aspirin, unless aspirin is contraindicated

10. Anticoagulants

10.1. Heparin

The initial approach to thrombosis in the APS is identical to any other thrombosis. For acute thrombotic event, the first therapy is heparin. Low molecular weight (LMW) heparin has replaced unfractionated heparin as the standard of care. Warfarin is started simultaneously and the two agents are continued together for a minimum of 4-5 days until the international normalized ratio (INR) rises to the desired therapeutic range i.e. 2.0 to 3.0 for two consecutive days.

Heparin also plays a critical role in the treatment of APS during pregnancy as warfarin is contraindicated in that situation. Several LMW heparins are available for clinical use. Most of the patients can be managed on outpatient basis except following 4 conditions :

- Massive DVT
- Symptomatic pulmonary embolism
- High risk of bleeding with anticoagulant therapy
- Presence of co-morbid conditions or other factors needing indoor care

There are situations where unfractionated heparin is preferred. Unfractionated heparin is short acting and its action can be quickly reversed with protamine. LMW is not completely reversible with this approach. Hence, whenever there is extra risk of bleeding, unfractionated heparin is preferred.

10.2. Warfarin

Once the patient is stabilized, except during pregnancy, warfarin is the standard of care for the long-term management of patients with APS. The current standard of care, developed through randomized controlled trials, is to maintain the INR between 2.0 and 3.0. Initial suggestion regarding high-intensity therapy and maintaining INR in the higher range has had no demonstrable benefit and is potentially harmful. The optimal duration of anticoagulation therapy using warfarin following a first thrombotic event is uncertain. Lifelong therapy is prudent for many patients. If, for some reason, warfarin has to be discontinued, low-dose aspirin is warranted.

If patients on warfarin therapy and having INR in the desired range of 2.0 to 3.0, developed thrombotic events, the treatment alternatives include increasing the target INR (3.0 to 4.0) or adding low-dose aspirin. There is no good data on comparative efficacy of these two options. There is no role of adding low-dose aspirin to warfarin therapy in patients whose INR is kept between 3.0 and 4.0. aPL may create problems in monitoring the INR. This can be helped by measuring chromogenic factor X levels or the prothrombin-proconvertin time instead of the INR. Measurement of F1 and/or F2 prothrombin fragment is another option. In practice, such patients are often treated with lower dose warfarin plus aspirin or with LMW heparin.

Self monitoring using portable testing equipments at home is feasible. Appropriately trained patients who self-monitor and self-adjust their oral anticoagulation have superior outcome i.e. fewer thromboembolic events, fewer episodes of major bleeding and a lower mortality.

10.3. Hydroxychloroquine

Hydroxychloroquine is a useful agent in patients with APS. It reverses platelet activation induced by aPL. Its potential utility in preventing APS-related events has been specifically shown in patients with SLE associated APS.

11. Specific clinical settings

11.1. Primary prophylaxis

Primary prophylaxis i.e. treating subjects with APS without clinical events includes aspirin, hydroxychloroquine, avoidance of oral contraceptives and taking care of various risk factors for arterial or venous thrombosis.

Primary prophylaxis with aspirin in patients with primary APS has doubtful efficacy. The conclusions drawn from the antiphospholipid antibody acetylsalicylic acid (APLASA) study are

- Asymptomatic individuals who are persistently positive for aPL, have a low annual incidence of acute thrombosis
- These individuals do not benefit from low-dose aspirin
- Thrombotic events in this population are unlikely in the absence of additional risk factors for thrombosis.

However, in patients with SLE and secondary APS, there is a greater role of aspirin prophylaxis. Such patients have distinct increase in episodes of thromboembolism and foetal wastage and low-dose aspirin significantly reduces such events. Concomitant use of hydroxychloroquine (6.5 mg/k/d) is a useful option.

Women with aPL should avoid oral contraceptives, especially those containing higher amount of estrogen. Other risk factors which predisposed to thrombosis should also be taken

care of. These include smoking, hypertension, hyperlipidemia and venous stasis.

12. Secondary prophylaxis

After an episode of thromboembolism, recurrent events occurred in 11% of patients per year. Some patients have multiple recurrences. Potentially devastating nature of these events is a strong argument for long-term and preferably lifelong anticoagulation in such patients.

Warafrin therapy together with low-dose aspirin is a reasonable treatment for patients having ischemic stroke or transient ischemic attack (TIA). Same applies to patients with cardiac manifestations i.e. myocardial infarction, cardiac valvulopathy and other ischemic events.

13. Thrombocytopenia

Mild thrombocytopenia requires no treatment. Clinically significant thrombocytopenia is best treated in a manner similar to those with chronic immune thrombocytopenic purpura i.e. corticosteroids, rituximab, intravenous Gammaglobulin, anti D etc. Occasional patients developed thrombotic thrombocytopenic purpura / haemolytic uremic syndrome and they are best treated with plasma exchange.

14. Catastrophic APS

A small subset of patients with APS has widespread thrombotic disease with visceral damage. This is referred to as catastrophic APS. Prognosis of these patients is poor. They can be helped by intensive treatment using combination of anticoagulation, corticosteroids, plasma exchange and intravenous immunoglobulin. Such treatment has recovery rates ranging from 50 to 80%. Precipitating factors should be taken care of

15. Investigational treatment

Investigational therapies for APS include rituximab and autologous stem cell transplantation

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