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Review Article

Antiphospholipid antibody syndrome

Jyoti R. Parida [a], Durga Prasanna Misra [a], Anupam Wakhlu [b], Vikas Agarwal [a,*]

[a] Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

[b] Department of Rheumatology, King George's Medical University, Lucknow, Uttar Pradesh, India

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ABSTRACT

Antiphospholipid antibody syndrome (APS) is characterized by recurrent pregnancy losses and/or thrombotic events (both arterial and venous) with persistently positive lupus anticoagulant or antiphospholipid antibodies. Activation of complements, platelets and endothelial cells by the anticardiolipin-β2GP-1 complex plays a major role in pathogenesis of thrombosis. Treatment is with anticoagulation (warfarin/heparin), with steroids needed in the presence of catastrophic APS or cytopenias. Upto a third of patients may have significant long term morbidity.

1. Introduction

Antiphospholipid antibody syndrome (APS), also referred to as antiphospholipid syndrome or Hughes syndrome, is characterized by recurrent pregnancy loss and or/thrombosis (venous, arterial or both), in the persistent presence of antiphospholipid antibodies {moderate-to-high titer IgM or IgG antiphospholipid antibodies-aPL; anti-β2Glycoprotein-1 (β2GP-1) or positive lupus anticoagulant test}. In addition, other clinical features like thrombocytopenia, hemolytic anemia, cardiac valvular lesions, dermatologic, renal and neurologic manifestations, as well as other antiphospholipid antibodies may be present, although they are not included in the classification criteria. APS may be primary, or secondary to connective tissue diseases as systemic lupus erythematosus (SLE). It is a significant contributor to pregnancy morbidity and thrombotic events in young adults.

1.1. *Epidemiology*

Antiphospholipid antibodies may be found in upto a tenth of healthy adults at low titers and up to 1% of the population may have moderate-to-high titer positivity. A tenth of stroke patients have been described to have aPL, with a higher proportion (nearly 30%) of young stroke patients harboring these antibodies. A fifth of women having three or more consecutive pregnancy losses, and upto one-seventh

* *Corresponding author*. Fax: +91 5222668812.
E-mail addresses: vikasagr@yahoo.com, vikasagr@sgpgi.ac.in (V. Agarwal).
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of patients with recurrent venous thrombosis harbor, aPL.[1–6]

1.2. *Classification criteria*

International consensus criteria for the diagnosis of APS were first proposed in 1998(Sapporo criteria), and later modified in 2004 (modified Sapporo criteria or Sydney criteria). These separately include clinical and laboratory criteria. Clinical criteria require presence of any one of:

1) Vascular thrombosis (one or more episodes), whether arterial, venous or small vessel thrombosis or
2) Pregnancy morbidity in the form of any of
   a) One or more loss of a morphologically normal fetus at or after 10 weeks of gestation.
   b) One or more preterm delivery of a morphologically normal baby (before 34 weeks gestation) due to pre-eclampsia/eclampsia/proven placental insufficiency.
   c) Three or more unexplained pregnancy losses before 10 weeks gestation after parental chromosomal and maternal structural or hormonal abnormalities have been excluded.

Laboratory criteria require the persistent presence (repeated at greater than 12 weeks but within 5 years interval) of any one of these abnormalities

a) moderate-to-high titer IgM (>40 MPL) or IgG (>40 GPL) aPL, >99th percentile, by a standardized ELISA.
b) anti-β2GP-1 antibody, IgM or IgG, >99th percentile, by a standardized ELISA
c) Lupus anticoagulant measured according to the guidelines set forth by the International Society on Thrombosis and Hemostasis.

Definite APS is diagnosed when at least one each of clinical and laboratory criteria are satisfied.

The modified Sapporo criteria differ from the original in increasing the minimum interval between tests from 6 weeks to 12 weeks, reiterating the need for persistent presence of these antibodies as opposed to transient aPL positivity due to infections, vaccines, drugs or environmental triggers and including anti-β2GP-1 antibody in the classification criteria. Also, they exclude patients with confounding factors (male>55years, female>65 years) and don't distinguish between primary and secondary APS. It must be noted that these are merely classification criteria and not necessarily applicable to the individual patient, who may or may not have the above described clinical features but have other features like cardiac vegetations or hematologic manifestations and satisfy laboratory criteria; vice-versa the clinical features as described in the criteria may be present but the antibodies present may be to other antigenic targets described in literature. Hence it needs emphasizing that clinician judgment is of utmost importance for the diagnosis in an individual patient, whereas classification criteria are meant for homogenization of literature reported or described with respect to a particular condition.[7–11]

2. Laboratory assays

2.1. *Lupus anticoagulant (LAC)*

LACs are determined by functional assays. Activated Partial Thromboplastin Time (APTT) tests the integrity of 'intrinsic and common' coagulation pathways. This test requires coagulation factors: I, II, V, VIII, IX, X, XI, & XII, phospholipids, calcium and an activator of coagulation (silica, kaolin etc). In presence of LACs, which bind to phospholipids, there is deficiency of phospholipids and thus clot formation is delayed leading to prolonging of APTT. It is not correctable by mixing with platelet-poor plasma from a healthy donor (as platelets can serve as a source of phospholipids) but corrects with addition of excess phospholipids (suggesting phospholipid dependence) to the exclusion of other inhibitors. To reduce risk of false positives, 2 tests are used viz. a diluted Russell Viper Venom Test (dRVVT) and an APTT with silica as the activator and low phospholipid concentration. dRVVT utilizes the property of venom of the Russel viper leading to direct activation of the factor X to Xa. However, in absence of phospholipids (due to binding with LACs) the clot formation is delayed. This again gets corrected by adding phospholipids rather than mixing with normal plasma. The disadvantages of LAC are its complicated methodology and labor intensive nature, hence limiting its availability to labs with the requisite expertise to perform it.[12,13]

2.2. *Antiphospholipid and anti-β2GP-1 antibodies*

Both are measured by standardized ELISA kits, hence enhancing their availability. They are considered positive if values lie at greater than 99th percentile of the population range, which is generally >40 MPL of IgM aCL and >40 GPL for IgG aCL, and varies from laboratory to laboratory for anti-β2GP-1 antibodies (in our laboratory, we take a cut off of 24). It must be emphasized that laboratory tests for APS need to be persistently abnormal at intervals of at least 12 weeks, because a variety of infections (EBV, CMV, HIV, HCV) and other unidentified environmental triggers can initiate aPL formation, which are transient and generally non-thrombotic as they do not have affinity for anti-β2GP-1.[12,13]

Presence of LACs in young women has been associated with 40 times greater risk of myocardial infarction, 5 times greater risk of stroke and increased incidence of miscarriage before 24 weeks of gestation. Moderate-to-high titer aCL positivity (IgM or IgG) has been linked to increased risk of miscarriage, and increased thrombosis on background of SLE. Elevated titers of anti-β2GP-1 antibodies per se increase incidence of stroke, and in the presence of concomitant LAC positivity, increase thrombosis risk. Triple positivity for aCL, anti-β2GP-1 antibodies and LAC has the highest thrombosis risk of all the above described situations, with upto 30% of these patients developing thrombotic events despite being on anticoagulation.[10,14–17]

In the absence of positivity for standard antibodies in the appropriate clinical context, it is worthwhile measuring other described antibodies as IgA IgM or IgG aCL, IgA anti-β2GP-1 antibodies, anti-prothrombin antibodies (aPT),