ANTIPHOSPHOLIPID SYNDROME AND LUPUS ANTICOAGULANT

CLINICAL BACKGROUND

Antiphospholipid syndrome (APS) is an autoimmune disorder in which autoantibodies are directed against phospholipid-protein complexes. APS is characterized by thrombosis (arterial, venous or small vessel) and/or pregnancy complications and persistently positive tests for antiphospholipid protein (aPL) antibodies. aPL antibodies are often classified as either lupus anticoagulant (LA), anticardiolipin (aCL) antibodies or anti-beta-2 glycoprotein 1 (β2GP1) antibodies.

Epidemiology:

Prevalence:

- aPL antibodies are an acquired thrombotic risk factor
- Present in a small percentage of young healthy subjects (1-5%) and in up to 10% of patients with venous thrombosis
- Estimates of prevalence are hampered by the variety of testing systems available for diagnosis
- Higher prevalence in patients with connective tissue disease, but most patients with aPL antibodies do not have an underlying autoimmune disease

Associations:

- Systemic lupus erythematosus (SLE) – up to 50% of patients
- Other autoimmune disorders
- Malignancy
- Liver disease
- Vascular disease

Risk Factors:

- Connective tissue disease (e.g., SLE)
- Infections – no increase in thrombotic risk
- Medications: chlorpromazine, procainamide, hydralazine – increased thrombotic risk

Pathophysiology and Basis for Laboratory Tests:

- Proposed mechanisms for thrombosis include endothelial cell damage or activation, platelet activation and interference with the function of anticoagulant proteins
- LAs are autoantibodies that target complexes of phospholipids with either β2GP1 or another plasma protein such as prothrombin
- LAs usually demonstrate an inhibitor effect in laboratory clotting tests by interfering with phospholipid-dependent clotting reactions
- Prolongation of clotting times (apparent anticoagulation) is an in vitro laboratory phenomenon; in vivo thrombosis is much more common than bleeding
- APS patients may have LA activity, positivity to aCL and/or β2GP1 IgG and IgM antibodies
- Thrombosis appears to be more common in patients with LA activity
- Positivity for all three (LA activity, aCL and β2GP1 antibodies) is a strong independent risk factor for thrombosis
- Transient aPL antibodies may occur in association with infections and with certain medications (procainamide, hydralazine, quinidine, chlorpromazine, penicillin)

Clinical Presentation:

- Venous, arterial, or small vessel thrombosis and/or obstetric complications
- Other potential abnormalities include cytopenias or other hematologic disorders and neurologic, dermatologic or cardiopulmonary abnormalities
- Catastrophic APS (CAPS) is a multi-organ illness caused by diffuse small vessel thrombosis and tissue ischemia

Treatment:

- Treatment decisions depend on the extent of clinical symptoms and may range from no treatment to long-term anticoagulation therapy

DIAGNOSIS

Indications for Testing:

- Recurrent vascular thromboses, recurrent pregnancy loss, unexplained prolonged PTT in an asymptomatic patient (indication for lupus anticoagulant testing)
- Additional indications for testing may also include the presence of endocarditis, livedo reticularis, thrombocytopenia, hemolytic anemia and thrombotic micrangiopathy

Criteria for Diagnosis:

Revised classification criteria for the antiphospholipid syndrome (International Society on Thrombosis and Haemostasis) 2006.

At least one clinical and one laboratory criterion must be met.

Clinical criteria:

1. Vascular thrombosis – One or more clinical episodes of arterial, venous or small-vessel thrombosis in any tissue or organ validated by imaging studies or histopathology
2. Pregnancy morbidity:
   a. One or more unexplained deaths of a morphologically normal fetus after 10th week of gestation
   b. One or more premature births of a morphologically normal neonate before the 34th week of gestation due to preeclampsia, eclampsia or placental insufficiency
   c. Three or more unexplained, consecutive, spontaneous abortions before 10th week of gestation, and with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

Laboratory criteria (at least one positive test on two or more occasions at least 12 weeks apart):

1. Lupus anticoagulant: detected in plasma according to the guidelines of the International Society on Thrombosis and Hemostasis
2. aCL antibody: IgG and/or IgM isotype present in a medium or high titer (>40 GPL or MPL or >99th percentile), measured by standardized ELISA
3. Anti-β2GP1 antibody: IgG and/or IgM isotype in high titer (>99th percentile), measured by standardized ELISA

GPL – IgG phospholipid antibody; MPL – IgM phospholipid antibody; ELISA – enzyme-linked immunosorbent assay

Laboratory Testing:

- Current recommendations for first-line laboratory testing include the following:
  1. LA activity. At least two phospholipid-dependent clotting assays, based on different principles, should be performed to identify LA activity. These two assays typically include a dilute Russell Viper Venom Time (dRVVT) and another PTT-based assay such as a Silica Clotting Time (SCT).
  2. aCL IgG and IgM antibodies
  3. β2GP1 IgG and IgM antibodies
- Repeat positive laboratory tests after 12 weeks to confirm persistent positivity
- Repeat testing if a strong clinical suspicion exists for APS but laboratory tests are negative

SCREENING

- Not recommended for patients with single deep vein thrombosis (DVT) unless a risk factor is present
- Test for antibodies in the following situations:
  - Thrombosis:
    - Arterial thrombosis <50 years
    - Unprovoked venous thrombosis <50 years
    - Recurrent thrombosis
    - Thrombosis at unusual site
    - Patients with both arterial and venous thrombotic events
    - Patients admitted with thrombotic microangiopathy of unknown etiology
  - Obstetric manifestations:
    - ≥One unexplained fetal loss after 10th week of gestation
    - Unexplained severe intrauterine growth restriction
    - Early or severe preeclampsia
    - ≥Three spontaneous miscarriages before 10th week of gestation
  - Patients with SLE:
    - Perform baseline test
    - Repeat testing
      - Before pregnancy, surgery, transplantation and use of estrogen-containing treatments
      - Presence of a new neurologic, vascular or obstetric event

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