

COAGULATION UPDATE

Issue #1 2011

Update on Lupus Anticoagulant and Antiphospholipid Antibody Syndrome

Irina Chibisov, MD, Hemostasis and Thrombosis Clinic ITxM Diagnostics,
Assistant Professor of Pathology, University of Pittsburgh Medical Center

INTRODUCTION

Lupus anticoagulants (LAC, or lupus inhibitors) are immunoglobulins/antibodies that bind to phospholipids and proteins associated with the cell membrane. Persons with these antibodies may have an abnormally high risk of blood clotting.

Antiphospholipid antibody syndrome is classified as primary or secondary depending on its association with other autoimmune disorders. Lupus anticoagulants are usually found in persons with autoimmune diseases, such as systemic lupus erythematosus, inflammatory bowel disease (Crohn's disease and ulcerative colitis), infections, and certain tumors. They may also be found in persons who take certain medications, including phenothiazines, phenytoin, hydralazine, quinine, and some antibiotics. Primary antiphospholipid antibody syndrome is diagnosed in patients demonstrating the clinical and laboratory criteria without other recognized autoimmune disorder.

A diagnosis of antiphospholipid antibody syndrome (APS) can be established in patients who meet at least one of the clinical criteria (vascular thrombosis or pregnancy complications) and one of the laboratory criteria discussed below.

Clinical Diagnostic Criteria:

1. Vascular thrombosis: one or more episodes of arterial, venous or small vessel thrombosis confirmed by imaging, Doppler studies or histopathology (thrombosis without significant inflammation in the vessel wall)

1. Pregnancy morbidity:

- a) One or more fetal death of morphologically normal fetus > 10 weeks gestation documented by ultrasound or direct examination.
- b) One or more premature birth of a morphologically normal neonate <34 week

gestation because of severe preeclampsia or severe placental insufficiency.

- c) Three or more unexplained fetal losses <10 weeks gestation with excluded anatomic, hormonal and chromosomal (maternal and paternal) abnormalities.

Non-criterion Clinical Manifestations of Antiphospholipid Antibody Syndrome.

- Hematologic: thrombocytopenia, hemolytic anemia, Evans syndrome, thrombotic microangiopathic hemolytic anemia.
- Cutaneous: livedo reticularis rash, cutaneous necrosis, digital gangrene.
- Neurologic: seizures, chorea, transverse myelitis, multiple sclerosis-like syndrome.
- Cardiac: mitral, aortic insufficiency, cardiac valve lesions.
- Renal: nephropathy with glomerular necrosis, cortical necrosis, renal infarction.

Laboratory Diagnostic Criteria:

The confirmation of diagnosis of the APS relies on laboratory tests. Current classification criteria for definite APS mandate the use of three "standardized" laboratory assays to detect antiphospholipid antibodies (IgG and IgM anticardiolipin and/or anti-beta 2 GP I antibodies) and/or a lupus anticoagulant (LAC), when at least one of the two major clinical manifestations (thrombosis or pregnancy losses) are present.

1. **A lupus anticoagulant** defined by a functional, clot-based assay using International Society on Thrombosis and Hemostasis (ISTH) guidelines identified in plasma on two or more occasions at least 12 weeks apart.

ISTH criteria for Lupus Anticoagulant:

- Prolongation of a phospholipid-dependent screening assay (eg aPTT, dRVV)
- Evidence of inhibitory activity on mixing studies with normal pooled plasma.

- Evidence that inhibitory activity is phospholipid dependent; and
- Exclusion of other coagulopathies.

2. Anticardiolipin IgG or IgM antibody in medium or high titer on two or more occasions at least 12 weeks apart measured by standardized ELISA.

3. Anti-beta-2 glycoprotein I IgG or IgM antibody in medium or high titer on two or more occasions at least 12 weeks apart measured by standardized ELISA.

Although International Consensus Guidelines for the determination of LAC have been published and revised, the existence of "standardized" tests for detection of anticardiolipin and anti-beta 2 GP I antibodies has remained elusive. In spite of the publication of several proposals, consensus documents and expert opinions, significant inter-assay and inter-laboratory variation in the results still exists, which affects the consistency of the diagnosis of APS.

Testing for anticardiolipin antibodies may be complicated due to:

- Broad intra and inter assay variability.
- Lack of standardized normal or abnormal control samples.
- Results may not correlate with thrombotic risk.
- Not specific for the syndrome and common in certain populations.

Positive anticardiolipin antibodies are seen in:

- Normal individuals 2-5%
- Normal Pregnancy 1-10%
- Elderly (>70 years of age) > 50%
- Patients with SLE 17-86%
- Patients with venous thrombosis 2-120%

Additional factors that complicate diagnosis:

- Pre-test analytical variables (importance of platelet-poor plasma)
- Sensitivity and specificity vary for different assay types and platforms.
- Limitations of testing while patients are on anticoagulants (including heparin, Coumadin, but more importantly direct thrombin inhibitors which frequently result in false positive results).
- Limitations of testing during acute setting.
- Difficulties with results interpretation

LAC testing should be considered in patients with the following profile.

High probability: Unprovoked VTE, unexplained arterial thrombosis in young patients, thrombosis in unusual locations, late pregnancy loss, or these symptoms in patients with an underlying autoimmune disease.

Moderate probability: Evaluation of prolonged aPTT, provoked VTE in a young patient, recurrent early fetal loss.

Low probability: Venous or arterial thromboembolism in elderly patient.

Treatment.

In patients with positive laboratory findings for LAC, but no symptoms of thrombosis, no treatment is usually recommended. If clots occur, blood thinners (heparin followed by warfarin) should be initiated. Anticoagulation with moderate-intensity warfarin (INR of 2.0-3.0) reduces the risk of recurrent venous thrombosis and may be effective for preventing recurrent arterial thrombosis. No evidence exists that high-intensity warfarin (target INR >3.0) is more effective than moderate-intensity warfarin. For patients with positive antiphospholipid antibody test result and prior stroke, aspirin and moderate-intensity warfarin appear equally effective for preventing recurrent stroke. Evidence is conflicting for treatment of patients with antiphospholipid antibodies and noncerebrovascular arterial thrombosis and recurrent thrombosis despite warfarin therapy. For women with antiphospholipid antibodies and recurrent fetal loss antepartum prophylactic LMWH combined with aspirin is recommended.

SUMMARY

APS is characterized by clinical manifestations of arterial or venous thrombosis, pregnancy complications and laboratory findings. Some patients with positive LAC studies may have no clinical manifestations. Testing for LAC should probably be limited to patients with high or moderate probability. Other considerations should include difficulties of testing interpretation due to inter-assay and inter-laboratory variation, limitations of testing at the time of acute thrombosis and during anticoagulation therapy. Confirmatory testing for lupus anticoagulant should be performed 12 weeks apart. If possible, testing of anticoagulant therapy should be considered. Testing should include standard lupus anticoagulant panel plus IgG and IgM anticardiolipin and anti-beta 2 GP I antibodies.

REFERENCES

1. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* Feb 2006;4(2):295-306
2. Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. *JAMA.* Mar 1 2006;295(9):1050-7.
3. The American College of Obstetricians and Gynecologists. Antiphospholipid Syndrome. *ACOG Practice Bulletin.* January/2011;118:1-8.
4. 13(th) International Congress on Antiphospholipid Antibodies (April 13-16, 2010, Galveston, TX), 2011 American College of Rheumatology.

Copyright ©2011, Institute for Transfusion Medicine

For questions about this *Coagulation Update*, please contact: Irina Chibisov, MD at: ichibsov@itxm.org 412-209-7350. Copies of the *Coagulation Update* can be found on the ITxM Diagnostics web page at www.itxmiagnostics.org under Education.