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Clinical Guide - The Antiphospholipid Syndrome (June 2004)

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1. DEFINITION

The antiphospholipid syndrome (APS) is increasingly recognized as an important clinical disorder, but one which has engendered confusion in both its clinical and laboratory aspects.

A diagnosis of APS requires the presence of both clinical and laboratory criteria (1,2).

Clinical Criteria:

- Thrombosis
    - arterial
    - venous
    - small vessels
- Obstetrical complications
    - fetal loss at 10 weeks or later, without apparent fetal abnormalities
    - premature birth (@ 34 weeks) due to pre-eclampsia or placental insufficiency
    - 3 or more consecutive unexplained spontaneous abortions (less than 10 weeks)

The manifestations of APS are similar whether the condition is primary, or whether it occurs in the setting of underlying connective tissue disease (e.g. lupus erythematosus) in which case it is referred to as "secondary" APS.

The clinical manifestations associated with APS can be caused by many different underlying disorders. Laboratory evaluation is critical to determine whether a clinical event is attributable to APS in a given patient.

Laboratory criteria:

Many laboratory tests have been used to detect antiphospholipid antibodies. These fall in two general categories: coagulation assays and antibody binding assays.

Lupus anticoagulants: An antibody that interferes with a phospholipid-dependent coagulation test is referred to as a "lupus anticoagulant" (LA). This is a misnomer. In practice most cases of LA have nothing to do with lupus erythematosus, many patients with lupus erythematosus do not have evidence of lupus anticoagulants, and these antibodies rarely exhibit an anticoagulant effect in vivo.

Anticardiolipin antibodies (aCL): Antibodies identified in assays of this type may bind directly to phospholipids or, more commonly, to other proteins bound to phospholipids, of which b2-glycoprotein I appears to be the most important.

- The diagnosis of APS requires at least one of the clinical criteria plus the presence of either a LA or an aCL.
- The LA or aCL must be shown to persist for at least six weeks before the diagnosis of APS may be made.

2. LABORATORY TESTING

When investigating patients with thrombosis for suspected hypercoagulability, other investigations, in addition to tests for antiphospholipid antibodies, are generally in order. As APS is not a hereditary condition, antiphospholipid antibody tests are not indicated in the work up of familial hypercoagulability. Please refer to the guideline, "Investigation of Hypercoagulable States".

Lupus anticoagulant assays

Clinical laboratories should offer lupus anticoagulant testing as a specific service. Because of the variable effects of lupus anticoagulants on different assays, laboratories should perform at least two different coagulation-based tests (1). Numerous tests for LA are available including:

- APTT. The most widely used test is the aPTT, performed using a sensitive reagent. Note: Although a prolonged aPTT may reflect a LA, the sensitivity of aPTT reagents to prolongation by LA is highly variable and different reagents will give different results for individual patients with APS. Hence, a normal aPTT obtained with a standard reagent does not rule out a LA.
- dilute Russel viper venom time (DRVVT)
- dilute prothrombin time
- thromboplastin inhibition test

LA are more strongly associated with thrombosis than are aCL.

Anticardiolipin assays

The aCL is an ELISA type assay, and is usually performed with separate assays for IgG and IgM antibodies. Although several variations on this test have been described, there is no consensus yet that other binding assays should be used in place of or in addition to the aCL in routine practice.

- Low titre aCL should not be considered diagnostic of APS.
- IgG aCL are more strongly associated with risk of thrombosis than are IgM aCL.

3. TREATMENT

Thrombosis

The immediate treatment of an acute thrombotic event in a patient with APS is the same as for other patients with thrombosis (usually anticoagulation with heparin or low molecular weight heparin). Low molecular weight heparin (LMWH) may be preferred in patients whose baseline aPTT is prolonged by a LA because of the difficulties monitoring unfractionated heparin in this situation. Alternately, unfractionated heparin may be used and monitored by heparin levels. There are no trial data to support the use of corticosteroids or other immunosuppressives in primary APS.

The risk of recurrent thrombosis in patients with APS is high. The controversial issues are the duration of the anticoagulation, the intensity of anticoagulation, and the best way to monitor warfarin. Consultation with a specialist is recommended for most patients with APS.

Duration: It is generally suggested that anticoagulation be continued indefinitely if the thrombotic event was otherwise unprovoked, though this has not been prospectively validated in clinical trials. It is not known whether anticoagulation may be stopped safely if the laboratory criteria for APS are no longer present on later follow-up; this approach seems most reasonable in patients with primary APS and repeatedly negative tests on follow-up.

Intensity: Most patients with venous or arterial thrombosis and APS do well with conventional warfarin treatment (target INR 2.0 - 3.0) (3). It is recommended that patients with recurrent thrombosis despite conventional doses of warfarin should maintain an INR of 3.0 - 4.0. This recommendation is based on one descriptive study (4) and requires confirmation by randomised trials. The benefit of adding aspirin in arterial disease is not clear, and is likely to increase the risk of bleeding.

Monitoring: Occasionally, a LA will prolong the INR. In such patients, alternate monitoring approaches may be necessary (5).

Pregnancy

For women with APS-associated complications of pregnancy, prophylaxis with LMWH or heparin, with or without ASA, can be recommended on the basis of randomized controlled trials showing improved pregnancy outcomes.

Prophylactic LMWH or heparin for pregnant women with APS and previous thrombosis is recommended by extrapolation from the experience with other thrombophilic disorders, but this has not been specifically addressed in trials. Please refer to the guideline, “Thrombosis in Pregnancy.” Specialist referral is appropriate in either of these circumstances.

Although APS may be associated with a number of other manifestations such as thrombocytopenia and livedo reticularis, there is no evidence to support treatment with anticoagulants for those conditions. Anticoagulants are indicated for the treatment of thrombosis and prevention of pregnancy loss.

References

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