Saint Luke's Regional Laboratories
Clinical Laboratory Letter
December 2013

Acetylcholine Receptor Antibody

Myasthenia gravis is an acquired autoimmune disease characterized by muscle weakness and progressive fatigability caused by autoantibody binding to the acetylcholine receptor (AChR) in the postsynaptic membrane of skeletal muscle. These antibodies block acetylcholine-binding sites, damage the postsynaptic membrane, and accelerate receptor degradation. Synaptic transmission fails when the autoantibodies cause a critical loss of the cation channel protein, which is required to activate the muscle action potential.

Three types of autoantibodies have been described; AChR binding, AChR modulating and striational. Physicians often order all three antibodies as part of a panel as well as MUSK antibodies. However, studies indicate that ordering all of these tests simultaneously is usually unnecessary.

AChR binding antibody is recommended as the initial case finding test because it is faster and more economical to perform. It is positive in ~90% of nonimmunosuppressed patients with generalized myasthenia gravis. AChR modulating antibodies are only indicated when AchR binding antibody is negative and when myasthenia gravis is mild, ocular restricted, or of less than one year duration. Striational antibody is recommended when both tests for muscle AChR antibodies are negative. Its primary clinical usefulness is to detect thymoma in patients who present with early onset of myasthenia gravis before the age of 45.

Patients with AChR antibody positive myasthenia gravis do not have MUSK antibodies. Therefore, MUSK antibody should only be ordered when patients test negative for AChR antibodies. Patients who are AChR-Ab negative and MUSK antibody positive tend to have a lower incidence of thymic hyperplasia and thymoma.

Antiphospholipid antibody syndrome

Diagnosis of antiphospholipid antibody syndrome (APS) is complex and requires fulfillment of both clinical and laboratory criteria.

Who should be tested?

Careful selection of patients who meet the clinical criteria mentioned below increases the pre-test probability of diagnosis of APS.

1. Individuals with unprovoked venous thromboembolism
2. Unexplained arterial thrombosis in young patients <50 years of age
3. Thrombosis at unusual sites
4. Late pregnancy loss
5. Any thrombotic event or morbidity in patients with other autoimmune disorders such as SLE

Additional criteria that are considered reasonable for testing include:

1. Patient with recurrent spontaneous early pregnancy loss
2. Provoked venous thromboembolism in young patient

Laboratory testing in elderly patients with arterial or venous thromboembolism is least helpful.

What laboratory tests are done for APS?

1. Clot based tests for lupus anticoagulant (APL)
    a. aPTT test with mixing studies and confirmation (HEX phase)
    b. DRVVT screen and confirmatory test
2. Antibody testing by ELISA
    a. Anticardiolipin antibodies (ACA)
    b. Anti-β2-glycoprotein 1 antibodies (B2GP1)

When to request APS testing?

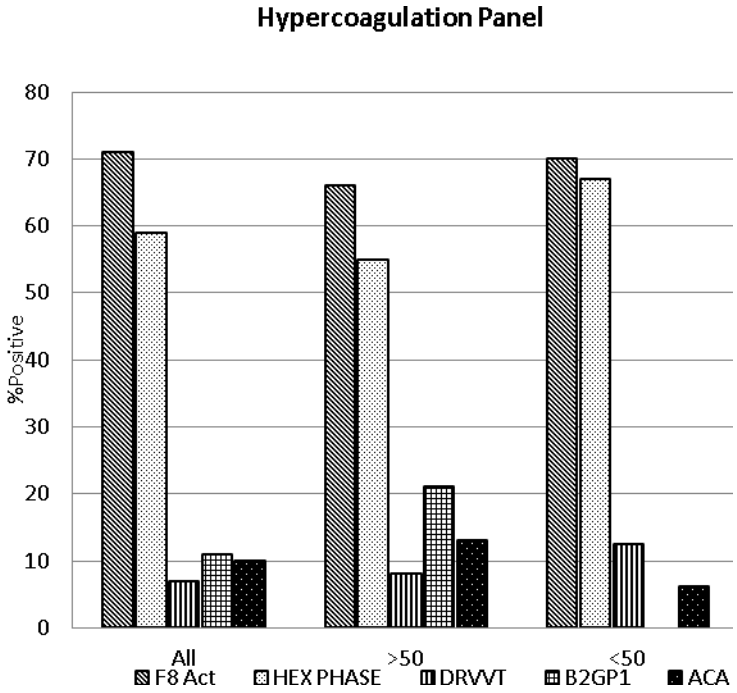
Ideally testing should be performed when the patient is clinically stable and not during the acute phase. The interpretation of laboratory tests can be difficult during the time of acute thromboembolic events because:

1. Acute phase reactants such as factor VIII and fibrinogen may be markedly increased altering clot-based testing such as APTT
2. Transient anti-cardiolipin antibodies may be present

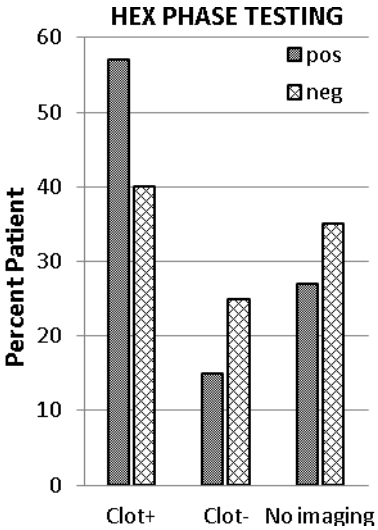
Ideally patient should be off anticoagulation therapy for at least 2 weeks and have an INR<1.5 prior to testing. If anticoagulant coverage is required, LMWH can be used which should be stopped 12 hours prior to testing.

Saint Luke's Experience

Recently we evaluated laboratory testing on a small group of patients who were investigated for hypercoagulability (n=42). The testing included protein S and C activity, factor VIII activity, prothrombin gene mutation, factor V leiden, HEX phase, DRVVT, and ACA and B2GP1 antibodies. Approximately >50% of the patients demonstrated high levels of factor VIII activity and positive HEX phase test with high levels of ACA/B2GP1 antibodies seen in less than 20% of the patients (please see graph below). Data pertaining to repeat testing for APL and/or ACA/B2GP1 antibodies, if performed was not available for analysis. The higher number of patients with a positive test was independent of age, which underscores problems associated with interpretation of clot based tests during acute phase of thrombotic episode.



Further analysis of lupus testing in relation to imaging performed for evidence of clot including ultrasound and CT revealed the percent positive HEX phase tests were not significantly different in patients with positive imaging versus negative and independent of age (see graph below).



Per recommendations by International Society on Thrombosis and Haemostasis (ISTH) the testing for antibodies including ACA and B2GPI should be done independent of outcome of clot-based test and repeated after 12 weeks to rule out transient increase during acute phase.

Based on these data, the clinical laboratory has come up with following algorithm for clot-based testing for APS.