Anti-thrombin III, you’re killing me

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Story from the Front Lines

A man in his 50s was seen in clinic for follow up. He presented to the emergency room six months prior with chest pain and shortness of breath. Chest CT showed a pulmonary embolism. The patient was started on heparin and transitioned to warfarin. He underwent testing one month later while on anticoagulation with cardiolipin IgA, IgM, and IgG; protein C & S activity levels; anti-thrombin III (AT III) activity level; factor V leiden genotyping; beta-2 glycoprotein IgG and IgM; and factor II prothrombin genotyping. The only abnormality was a slightly decreased AT III activity level of 75% (normal 76-128%). AT III testing showed 76% on repeat 2 weeks later. In clinic, the patient had been very anxious regarding his initial abnormal AT III activity level and was hesitant to stop anti-coagulation. AT III was rechecked a third time, after anti-coagulation was discontinued, and activity was normal at 84%. He chose to remain off anti-coagulation.

Teachable Moment

The diagnosis of venous thromboembolism (VTE) is followed by the clinical question, “why did this happen?” The principal goal is to determine the recurrence risk and reduce morbidity and mortality from another thrombotic event. Evaluation and treatment are relatively straightforward when thrombosis is attributed to an acquired or environmental effect, including estrogen therapy, malignancy, trauma, surgery, or immobility. If thrombosis is unprovoked, clinicians contemplate an evaluation to better assess the risk for recurrence and benefit from prolonged anticoagulation.

Testing for hereditary thrombophilia disorders include: factor V leiden genotyping, cardiolipin antibodies, protein C and S activity levels, prothrombin genotyping, beta-2 glycoproteins, and anti-thrombin III. Factor V leiden is the most common genetic risk factor for VTE.¹ Twenty percent of patients with a first event are heterozygous and 2% homozygous for factor V leiden. Prothrombin mutation prevalence in the general population is 1-3% and 9.7% in patients with a first VTE.² The prevalence of protein C & S deficiencies and AT III deficiency are negligible in both the general population and patients with a first VTE.³ Additionally, AT-III is autosomal dominant, but most patients are heterozygotes and not at higher risk for thrombosis with levels 40-60% of normal. Patients may also be tested for antiphospholipid syndrome (APLS) with lupus anticoagulant testing, anticardiolipin antibodies, and beta 2-glycoprotein levels.

Not only are hypercoagulability disorders uncommon, but the benefit of conducting a work-up is unclear. Hypercoagulability evaluation also presents several opportunity costs. Testing for these rare disorders is expensive and can be difficult to complete. Our patient, for example, required AT III testing three times because the first two tests were completed while on anticoagulation. Also, due to the high false positive rate, APLS testing should be repeated at least 12 weeks after initial testing. This can easily be overlooked and result in misdiagnosis and prolonged anticoagulation.
As clinicians, we want answers for our patients; however, no difference in outcomes has been demonstrated by evaluating for thrombophilia after one thrombotic event. Small, retrospective studies have shown no benefit. One study showed no statistical difference between VTE recurrence risk when patients with an initial idiopathic VTE were stratified based on outcome of thrombophilia evaluation.  
No randomized trials have been conducted to determine the recurrence risk of VTE with or without thrombophilia work-up and a Cochrane review was inconclusive due to the lack of trials.  
Ultimately, there is no strong evidence or strict guidelines to guide practitioners. We must minimize harm by deciding which patients should undergo evaluation when results will change our management and order appropriately timed testing. In our patient, he underwent evaluation despite his lack of risk factors for thrombophilia. Protein C, protein S, and AT III activity levels were then measured while on anti-coagulation. This patient was anxious for several months while undergoing repeat testing and deciding whether to continue anticoagulation for a possible increased risk in VTE recurrence. He would have benefited from completing a three month course of anticoagulation and then discussing the risks and benefits of hypercoagulability evaluation and chronic anticoagulation.

Thromboembolic disease remains an area where we must practice the art of medicine. Does evaluation of a few known hypercoagulability disorders give us as practitioners an indication to stop or continue anticoagulation? Will this ultimately affect my patient’s morbidity or mortality in the future? These queries rest on us, but this does not release us from the responsibilities of minimizing cost, stress, and ultimately harm to our patients.

References