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Hypercoagulablity Workup: Antithrombin Deficiency

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Introduction to Thrombophilia

Hypercoagulability is the main pathologic function needed to form a venous thrombosis (VT), a common cause of morbidity and mortality in many clinical settings. Thrombophilia is a disorder with an increased tendency to form clots, and it can be inherited or secondary to acquired risk factors, such as stasis or oral contraceptive pills. Clinical presentations favoring an inherited disorder include unexplained VT at young age (<50), unusual site of VT, recurrent or extensive spontaneous VT, recurrence of VT on anticoagulation, unexplained pregnancy loss (≥3 losses before week 10 or ≥1 loss after week 10), or family history of congenital thrombophilia or VT.[1] When clinical suspicion is high, it is important to screen for inherited disorders since it can direct lifelong anticoagulation, genetic screening and counseling for families, and risk stratification for VT. The primary differential diagnosis for inherited hypercoagulability includes protein S deficiency, protein C deficiency, antithrombin (AT) deficiency (ATD), prothrombin gene mutation, and factor V Leiden mutation causing activated protein C resistance. This article will focus on the mechanism and testing of antithrombin deficiency; details for other tests will be discussed in separate articles within a series.

Antithrombin Deficiency

Antithrombin deficiency (ATD) is an inherited thrombophilia, with a prevalence of 0.02% to 0.17% in the general population. In addition, ATD carries the highest risk of thrombosis among the inherited thrombophilias[2,3] ATD was first described in 1965 and since then, more than 127 genetic mutations have been identified. The inheritance pattern is autosomal dominant, with variable penetrance.[3] Antithrombin (AT) is an anticoagulant

protein that is generated in the liver and circulates in a latent state. When anticoagulation is necessary, AT is activated by endogenous heparan sulfate, located on the surface of endothelial cells. Exogenous heparin significantly amplifies AT's ability to inhibit coagulation.[1] Once activated by heparin, AT irreversibly binds with coagulation factors II, Xa, IXa, and IXa, while also inhibiting the downstream conversion of fibrinogen to fibrin. Lack of AT leads to a procoagulant state in which individuals are prone to develop thrombotic complications.

ATD can be classified into two types: type I and type II. Overall, type II ATD is more frequent in the population at large. However, type I ATD is more common amongst patients who develop symptoms. In type I deficiency, AT levels are low, leading to a decrease in both antigen level and functional activity. On the other hand, type II deficiency is a qualitative defect in which AT is dysfunctional. In these patients, AT antigen levels are normal but functional activity is decreased.[4] Type II deficiency can be further divided into subtypes IIa, IIb, and IIc based on the different mutated binding sites. This is clinically important since patients with type IIb deficiency are less likely to develop a thrombosis.[3]

Laboratory assessment of ATD involves measurement of AT activity (functional assay) and AT antigen levels (immunoassay) in a stepwise approach. To determine whether a deficiency is present, AT functional activity should be measured first. Next, AT antigen levels should be assessed, since this will distinguish between type I and type II ATD.([9]) Although molecular sequencing can be performed, the large number of potential mutations makes this test impractical for most cases.[5]

Ideally, testing AT functional activity should be performed approximately three months after the resolution of a thrombosis and after stopping both heparin and direct thrombin inhibitors.[4] A normal AT functional activity, especially during acute VT, rules out ATD. When testing reveals abnormally low AT functional activity, acquired ATD should be considered. Acquired ATD is far more common than inherited ATD and can be due to physiologic conditions or drug therapies. Thus, testing should be repeated at a later date, after clot resolution. Additionally, an abnormal AT functional activity level should be seen on at least two tests before diagnosing ATD.

Diagnosing a patient with thrombophilia has many consequences, including the need for lifelong anticoagulation. For patients with ATD, it is important to emphasize that family members are at an increased risk for thrombosis and may require hypercoagulability screening.[6] Because of these implications, ATD testing should only be performed after completing a careful clinical history and ruling out secondary interferences, such as liver disease, inflammatory bowel disease, estrogen therapy, or certain forms of chemotherapy.[1,4,7] After deciding to test for ATD, careful interpretation of results is essential.[8] Communication with the pathologist at your local hospital laboratory or reference laboratory can be helpful to determine what testing may be beneficial to a patient.

References

1. Foy P, Moll S. Thrombophilia: 2009 update. *Current Treatment Options in Cardiovascular Medicine*. 2009;11(2):114–128.

2. Cohn DM, Roshani S, Middeldorp S. Thrombophilia and venous thromboembolism: implications for testing. *Semin Thromb Hemost.* 2007;33(6): 573–581.

3. Patnaik MM, Moll S. Inherited antithrombin deficiency: a review. *Hemophilia*. 2008;14(6)1229–1239. doi:10.1111/j.1365-2516.2008.01830.x.

4. Kottke-Marchant K, Duncan A. Antithrombin deficiency: issues in laboratory diagnosis. *Arch Pathol Lab Med*. 2002;126(11):1326–1336.

5. Hepner M, Karlaftis V. Antithrombin. *Methods Mol Biol.* 2013;992:355–364. doi:10.1007/978-1-62703-339-8_28.

6. De Stefano V, Rossi E. Testing for inherited thrombophilia and consequences for antithrombin prophylaxis in patients with venous thromboembolism and their relatives. A review of Guidelines from Scientific Societies and Working Groups. *Thromb Haemost*. 2013;110(4):697–705. doi: 10.1160/TH13-01-0011.

7. Khor B, Van Cott EM. Laboratory tests for antithrombin deficiency. *Am J Hematol*. 2010;85(12):947–950. doi:10.1002/ajh.21893.

8. Middeldorp S. Is thrombophilia testing useful? *Hematology Am Soc Hematol Educ Program*. 2011;2011:150–155. doi:10.1182/asheducation-2011.1.150.

9. Johnson NV, Khor B, Van Cott EM. Advances in laboratory testing for thrombophilia. *Am J Hematol*. 2012;87 Suppl 1:S108–112. doi:10.1002/ajh.23186.