

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Thrombophilia Evaluation: The Value of Testing Relatives

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H&O When testing for inherited thrombophilia, what factors should physicians look for?

KB There are 5 inherited thrombophilias: factor V Leiden mutation, prothrombin G20210A mutation, protein S deficiency, protein C deficiency, and antithrombin deficiency. The factor V Leiden mutation is the most common mutation in Caucasian populations (affecting approximately 6% of the general US Caucasian population) and is much less common or absent in other ethnic populations. The second most common mutation is the prothrombin G20210A mutation, which is seen in approximately 2–4% of the general Caucasian population. The other 3 inherited thrombophilias—protein S deficiency, protein C deficiency, and antithrombin deficiency—are much less prevalent.

The above mentioned are the hereditary thrombophilias that I look for. There are other putative thrombophilias out there, such as elevated lipoprotein a or elevated factor VIII levels, hyperhomocysteinemia, or antiphospholipid antibodies, but I do not believe that they qualify as bona fide hereditary thrombophilias, and most appear to be acquired abnormalities. While I will routinely look for a lupus anticoagulant and/or elevated levels of antiphospholipid antibodies (either cardiolipin or beta2-glycoprotein I antibodies) in patients with idiopathic venous thromboembolism, relatives of thrombotic patients with antiphospholipid antibody syndrome should not be considered for testing.

Thrombophilias are most frequently dominant in terms of their inheritance with variable (and often

times very incomplete penetrance); in other words, they are heterozygous. There are some rare homozygous or compound heterozygous deficiencies with which people could have 2 abnormal copies of a given gene leading to thrombophilia, but the most common setting is a single abnormality.

H&O What are the clinical benefits and drawbacks to testing for inherited thrombophilia?

KB The benefits are not very clear. The 5 thrombophilias are bona fide risk factors for venous thromboembolism (VTE) and are found with increased frequency in people with documented VTE, particularly deep venous thrombosis and pulmonary embolism. Inherited thrombophilias are also risk factors for people with venous thrombosis in unusual sites such as cerebral vein thrombosis, portal mesenteric venous thrombosis, or even superficial thrombophlebitis.

There are 2 ways to approach the issue of testing patients with VTE: 1) Is there a benefit to widespread testing to identify patients who have not yet had an event to be at risk? The answer is an unequivocal “no.” We do not screen healthy people who have no personal or family history for venous thrombosis for these abnormalities. The rationale behind this is that the 2 most common abnormalities, the factor V Leiden and prothrombin G20210A mutations, have a very low clinical penetrance of venous thrombosis. Therefore, people who are carriers of these abnormalities—and there are many in the population—only have a 5–10% risk that they will ever have

a clot in their lifetime. When you consider the clinical impact and cost of doing widespread screening to identify patients with these thrombophilias, it just does not make sense. While the other 3 thrombophilias tend to have a higher clinical penetrance, they are much less frequent in the general population. Therefore, there is no reason to screen for hereditary thrombophilia if the patient has no personal or family history of a VTE.

2) Is there benefit in screening people who have actually had a venous thrombotic event? The answer would be an equivocal “no.” There are many people who have had a spontaneous thrombosis or venous thrombosis in association with risk factors such as oral contraceptive use or pregnancy. We know that there is a strong interaction between elevated female hormone levels and the hereditary thrombophilias. The issue of identifying a risk factor, while certainly of academic interest and perhaps some value to the patient to know why they had a clot, generally does not affect their management and therefore may not be necessary. The ramifications of most of the hereditary abnormalities, in terms of whether a physician should manage them any differently based on whether or not an abnormality was found, are controversial.

Most of the evidence indicates that clinical risk factors at the time of the thrombotic event are the major determinants of recurrence risk following an initial course of anticoagulation, particularly whether the initial clot was unprovoked or provoked. Presence of a hereditary thrombophilic defect really does not carry as much importance, particularly for those with unprovoked or spontaneous clots who are at substantial risk for recurrence. A factor V Leiden or prothrombin G20210A mutation does not add to the recurrence risk any more than just having an unprovoked event without one of these abnormalities. Therefore, finding either of these abnormalities really should not influence the duration of anticoagulation or how a physician should manage these patients going forward. By virtue of having had an unprovoked (spontaneous or idiopathic) event, a patient is already at significant risk of having another event and would need prophylaxis in high-risk situations, regardless of whether or not an abnormality is found.

Last but not least, there are downsides to testing. There is the potential of creating undue anxiety for the patient and asymptomatic relatives who are found to have an inherited thrombophilia; I have seen this happen in some of my patients. We also are running up costs with testing and the subsequent need for consultations, and there may still be insurance implications. The testing could result in an error—either in the laboratory testing itself or in the interpretation of the data. Moreover, someone who is found with an abnormality could be over

zealously counseled and may decide to not get pregnant or to be on heparin during pregnancy, even though the risk of thrombosis is quite low in carriers of the factor V Leiden or prothrombin G20210A mutations. With all this and the paucity of evidence showing improved clinical outcomes by testing people with the low penetrance thrombophilic disorders, I can come up with more negatives than positives for having this information. In any case, it will require access to someone knowledgeable on what the results of the testing mean or do not mean.

H&O Which patients should be tested for thrombophilia? Are there certain subsets of patients or cases that would more likely benefit from testing?

KB I believe that the only situation in which most everyone would screen is in people with a very strong family history of first-degree relatives having had an event—generally a “higher risk thrombophilia” (ie, these tend to be the rarer thrombophilias such as the antithrombin, protein C, or protein S deficiency). Also, some subtypes of antithrombin deficiency have a higher penetrance of thrombosis. Therefore, there is no argument against testing in people with a strong family history; this generally means one or more first-degree relatives who have had venous thrombotic events before the age of 50. The incidence of VTE does increase as people get older—a paradox because some of the weaker thrombophilias such as factor V Leiden and prothrombin G20210A mutation are risk factors for venous thrombosis in older healthy people; there is a genetic risk factor that is with them throughout life, and as people get older, the risk of VTE goes up as well. The longer you are exposed to the underlying genetic risk factor, the more years you are at risk, which contributes to the higher absolute risk of VTE; this risk rises steeply after age 60.

Given the present data, treatment decisions regarding the duration of anticoagulation and performance of hereditary evaluations become a very individualized clinical decision. For several of these disorders—antithrombin, protein C, or protein S deficiency—the diagnosis is sometimes made erroneously because they are done by quantitative measurements. We try to establish whether a heterozygous deficiency state is present by determining whether the levels of these proteins are approximately 50% of normal, but their large coefficients of variation in these assays sometimes contribute to erroneous diagnoses. It could be a laboratory problem, or it could result from drawing levels at the wrong time. For example, if you draw protein S or C levels in the midst of an acute thrombotic episode or when the patient is on warfarin or

heparin, we may get lower results that do not reflect the patient's baseline level.

H&O What are some things a physician should consider before testing relatives of patients with inherited thrombophilia?

KB The issue of whether or not to test relatives is ambiguous. Physicians are concerned about missing things, for which they can potentially be sued for malpractice. However, if you have a discussion about the pros and cons of thrombophilia testing with a patient, they can be a part of the decision-making process. However, many experts on thrombophilia are quite nihilistic about the benefits of widespread thrombophilia testing.

I believe that the rationale for testing should initially be directed to the actual patient who has had venous thrombosis, so that if and when you do screen the relatives, you will know what defect you should be looking for.

H&O What are some areas that need further investigation in testing for thrombophilia?

KB There are ongoing studies that address whether or not there is value in family testing. These studies are looking into risk profiles, diagnosis, and outcomes. However, there is already a fair amount of literature which, albeit not definitive, suggests that there is no benefit in the information obtained by hereditary thrombophilia testing being used clinically.

Additionally, there are researchers investigating the genome in patients with venous thromboembolism. Investigators are attempting to identify other genetic variants that increase thrombotic risk, by conducting genome-wide scans looking for modifier genes. The conventional view is that there are other modifier genes that will better allow us to risk stratify people going forward. However, unless the information is clinically useful in management, it is important to remember that patients may not want to know about these things.