Diagnosis and management of the hypercoagulable patient

Kenneth A. Bauer M.D.

From the Hematology-Oncology Section, Brockton-West Roxbury Department of Veterans Affairs Medical Center and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, U.S.A.

Programa Educacional del XIV Congreso Argentino de Hematología

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Prior to 1993, a cause of thrombophilia was detectable in a relatively small percentage of patients presenting with venous thromboembolism. Hereditary defects were found in only 5 to 15% of patients and were confined to deficiencies of antithrombin, protein C, and protein S[1]. There has recently been great interest in this area due to the discovery of two prothrombotic mutations prevalent in Caucasian populations, factor V-Arg506Gln or factor V Leiden[2] and the prothrombin G20210A mutation[3]. The factor V Leiden mutation results in resistance to activated protein C[4], and heterozygotes with the prothrombin G20210A mutation have prothrombin antigen and activity measurements which are elevated by approximately 30% compared to normal individuals[3]. Recent studies have also demonstrated that elevated plasma homocysteine levels constitute a risk factor for venous as well as arterial thrombosis[5]. These abnormalities along with the presence of markers of the antiphospholipid antibody syndrome (either a lupus anticoagulant or elevated cardiolipin antibody titers) can be identified in a substantial percentage of patients presenting with a first episode of idiopathic venous thromboembolism (i.e., in the absence of a triggering risk factor such as surgery, immobilization, or active malignancy). However with the exception of the antiphospholipid antibody syndrome[6], it is not clear whether the management of the majority of patients with hereditary thrombophilia should be any different from those without defects. The following discussion will therefore focus on the question of who should be screened for hereditary thrombophilia and the implications of such a diagnosis on patient management.

Among unselected patients presenting with an initial episode of idiopathic deep venous thrombosis, 12 to 20% of will be found to be heterozygous for the factor V Leiden mutation and 6% heterozygous for the prothrombin G20210A mutation as compared with 6% and 2% in asymptomatic control populations, respectively[3,7,8]. The identification of either of these diagnoses in the setting of acute thrombosis does not alter their initial anticoagulation regimen. Similarly, the initial management of thrombotic patients with a diagnosis of one of the less common thrombophilias, deficiencies of antithrombin, protein C, or protein S, is generally identical to patients without these defects. Also, erroneous diagnoses can easily be made by testing for these defects in the acute setting (se below). Thus it can be argued that there is little to be gained by immediately evaluating for the hereditary thrombophilias when patients present with their first thrombotic episode.

Standard therapy for patients with deep venous thrombosis and pulmonary embolism typically includes anticoagulation for a 3 to 6 month period with warfarin at an International Normalized Ratio (INR) between 2 and 3. However Prandoni et al.[9] have provided data that the cumulative incidence of recurrent venous thrombosis following the cessation of therapy in patients presenting with a first episode of symptomatic venous thromboembolism is 24.8% at 5 years and 30.3% at 8 years. Recurrences occur less frequently when the initial event is associated with surgery or trauma. A recent clinical trial in patients with a first episode of "idiopathic" venous thromboembolism (i.e., without a major precipitating factor) found that individuals randomized to 3

months of anticoagulation had a very high recurrence risk (27% per patient-year)[10]. Patients randomized to continue warfarin experienced a 95% reduction in risk of recurrent venous thromboembolism. Testing for prothrombotic defects would clearly be helpful if patients were identified who are particularly prone to recurrences and thus are candidates for long-term antithrombotic prophylaxis. Unfortunately there is presently conflicting data regarding whether the recurrence risk is higher among patients with a first episode of venous thromboembolism associated with the factor V Leiden or prothrombin G20210A mutations as compared to those without a prothrombotic mutation[10-15]. In other clinical settings such as arterial thrombosis where the data is ambiguous as to whether hereditary thrombophilia constitutes a risk factor, the ascertainment of such a diagnosis often proves problematic. The significance of a positive diagnosis may be inappropriately interpreted as necessitating anticoagulation where it might otherwise not be undertaken with its attendant bleeding risk. It is best therefore not to investigate for the hereditary thrombophilias in most patients who only have arterial thrombosis.

A number of arguments however can be advanced in favor of screening for the hereditary thrombophilias. These include and improved understanding of the pathogenesis of deep venous thrombosis or pulmonary embolism for both the patient and their treating physician if a specific prothrombotic defect is identified. This can benefit the patient's family by leading to the diagnosis of other affected relatives. This knowledge aides in focusing attention on antithrombotic prophylaxis during temporary periods of increased thrombotic risk (e.g., surgery, immobilization), a matter of particular relevance to women with hereditary thrombophilia whose risk of sustaining venous thrombosis is increased approximately 4- to 8-fold by oral contraceptive use and pregnancy[16, 17]. Women with hereditary thrombophilia are also likely at increased risk for venous thrombotic complications in association with hormone replacement therapy and tamoxifen[18-21]. In healthy older patients with idiopathic deep venous thrombosis, the identification of a hereditary prothrombotic defect helps mitigate concern regarding an underlying occult malignancy and the resulting tendency to undertake expensive diagnostic tests.

Thus we are faced with the paradox of being able to diagnose prothrombotic defects in ever growing numbers of patients presenting with venous thrombosis, but it is uncertain if, and how, the results of the tests in most patients should influence their care. Given that a complete laboratory evaluation for thrombophilia is costly, it is appropriate to test for thrombophilic defects based upon the patient's personal and family history and clinical evaluation. Due to the inaccuracy of clinical diagnosis, it is essential to verify that thrombotic events were documented by objective tests. Acquired causes of hypercoagulability should be sought such as major surgery, active malignancy, systemic lupus erithematosus, or a myeloproliferative disorder. The hereditary thrombophilias have not been identified at increased frequency in thrombotic patients with these disorders as compared to controls, and therefore testing in such patients is not routinely recommended. This is in contradis-tinction to venous thromboembolism in association with oral contraceptive use or pregnancy and the puerperium which frequently trigger venous throm-botic events in women with hereditary thrombo-philia[16, 17, 22].

Based on the patient's thrombotic history, it is useful to characterize patients as "strongly" or "Weakly" thrombophilic to help guide the extent of the laboratory evaluation. Patients are termed "strongly" thrombophilic if they sustained their first venous thromboembolic event prior to age 50, have a history of recurrent thrombotic episodes, or have first degree family members with documented venous thromboembolic events occurring before age 50. Should one or more of these features be present, a complete evaluation for hereditary thrombophilia is appro-priate. This includes testing for the factor V Leiden mutation, which is most often done by screening for resistance to activated protein C with a clotting assay and then confirming positive results by genetic analysis, and for the prothrombin G20210A mutation. "Strongly" trombophilic patients should also undergo testing for deficiencies of antithrombin, protein C, and protein S. While molecular diagnostic techniques are used to diagnose factor V Leiden and the prothrombin G20210A mutation, heterozygous deficiencies of antithrombin, protein C, and protein S result from many different mutations. These three abnormalities must therefore be diagnosed using specific assays. Low levels of antithrombin, protein C, or protein S deficiency however can occur in the setting of acute thrombosis making reliable diagnosis of a hereditary deficiency difficult. Furthermore antithrombin levels can be lowered in association with heparin therapy and levels of protein C and protein S are reduced by warfarin. It is therefore optimal to perform testing for these three deficiencies at least two weeks after the completion of anticoagulation. "Weakly" thrombophilic patients include individuals 50 years of age or older with a first episode of "idiopathic" venous thromboembolism in the absence of a positive family history. Among men over age 60 in the Physicians'

Health Study with a first episode of "idiopathic" venous thromboembolism, 26% had the factor V Leiden mutation[8]. Thus screening for this defect along with the prothrombin G20210A mutation has a reasonable diagnostic yield in such patients. On the other hand, the likelihood of establishing a diagnosis of hereditary antithrombin, protein C, or protein S deficiency in this population is so low (less than 5%) that screening for these defects can be omitted. Both "strongly" and "weakly" thrombophilic patients should undergo laboratory testing for the presence or markers of the antiphospholipid antibody syndrome and hyperhomocysteinemia. It is also appropriate to investigate for the presence of the these two entities in patients with unexplained arterial thrombosis.

With respect to management, it is generally recommended that asymptomatic patients with hereditary thrombophilia identified through family studies not receive chronic oral anticoagulation. However they should receive counselling regarding their diagnosis, the need for prophylaxis during high-risk situations, and symptoms that require immediate medical attention. As there have been no controlled trials of the duration of anticoagulant therapy in the hereditary thrombophilias, therapy must be tailored to the individual patient[23]. In patients with a first venous thrombotic events in the setting of a transient triggering factor, anticoagulation can be discontinued after 3 to 6 months if the triggering factor is no longer present. Patients with venous thromboembolism in the absence of triggering factors should be treated for 6 months. Criteria for indefinite anticoagulation include a single idiopathic venous thrombotic event in the presence of more than one genetic defect (e.g., homozygous factor V Leiden, combined heterozygosity for factor V Leiden and the prothrombin G20210A mutation, etc.), an initial life-threatening thrombosis (e.g., massive pulmonary embolism; cerebral, mesenteric, portal, or hepatic venous thrombosis), and two or more spontaneous thromboses. It is uncertain whether patients with a single genetic defect warrant indefinite anticoagulation after a first spontaneous episode of venous thromboembolism. Many clinicians with expertise in this area recommend indefinite anticoagulation for patients with heterozygous antithrombin deficiency as they appear more thrombosisprone than patients with other single heritable defects. Some also recommend such an approach for patients with heterozygous deficiencies of protein C and protein S. While prolonged anticoagulation at an INR of 2 to 3 is highly effective in preventing thrombotic recurrences, this benefit is partially offset by increased bleeding which can occasionally be fatal. Patients with the common thrombophilias, heterozygotes with the factor V Leiden or prothrombin G20210A mutation, should receive counselling regarding the approximate magnitude of the recurrence risk as well as the bleeding complications associated with chronic warfarin treatment. Given the present data regarding the overall benefits and risks of indefinite anticoagulation even in patients with two or more episodes of venous thromboembolism, well-informed patients can become active participants in the decision making process with their physician. Though fewer than 10% of strongly "thrombophilic" and 1% of weakly "thrombophilic" patients will be found to have multiple genetic defects, other prothrombotic mutations will likely be discovered in the coming years. This will hopefully enable us to identify a greater percentage of patients with multiple genetic defects who likely are at highest risk for recurrences.

There are presently several randomized clinical trials ongoing in patients with idiopathic venous thromboembolism to determine the efficacy of indefinite low intensity warfarin at an INR of 1.5 to 2 in preventing recurrent events. It is hypothesized that this regimen will provide significant antithrombotic protection, but less frequent major bleeding complications, so that the overall benefit of prolonged anticoagulation will be more favorable than today's conventional-intensity anticoagulation. As many patients accrued in these trials will turn out to have hereditary thrombophilia, it will be important to ensure that the conclusions of such studies are applicable to this population and that the efficacy of low-intensity anticoagulation is not reduced in these individuals.

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