Management of Thrombophilia: Who to Screen?

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Key Words

Thrombophilia · Thrombosis · Screening · Case-finding · Strategy · Risk

anticoagulant therapy can be made purely in relation to clinical criteria.

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Abstract

Testing for laboratory evidence of heritable thrombophilia is now common. This practice undoubtedly arose in response to association studies, which revealed the influence of heritable thrombophilic defects on the development of VTE. Now that high quality clinical outcome studies are being reported it is becoming apparent that despite association, testing has limited predictive value for the majority of unselected symptomatic patients. Clearly, there is a difference between the ability of a test to explain why one individual is more likely to suffer a thrombosis than another and the ability of the same test to predict which patients who have already had thrombosis are likely to suffer a recurrence. In the absence of grade A recommendations, it is inevitable that practice will vary. Decisions will be influenced by local resources, competing demands for clinical and laboratory services and not least the professional interest of the haematologist. If thrombophilia testing is performed there is a strong case for selecting patients for testing as in most cases decisions regarding intensity and duration of

Laboratory Tests for Heritable Thrombophilia

The issue as to who to test or screen for evidence of heritable thrombophilia is contentious. This is because there are no strong evidence based guidelines. For example in 2001 the British Society for Haematology produced an evidence based guideline on the management of thrombophilia [1]. Of the 19 recommendations there were no grade A recommendations and 16 were grade C. It is therefore not surprising that opinions differ [2,3]. Nevertheless, thrombophilia testing is now commonplace. In a 12 month period in the mid-1990s (1996/7) at least 25,000 tests for APC resistance were performed in the UK alone [4]. In the Cambridge Thrombosis and Haemostasis Centre thrombophilia testing increased exponentially in the 1990s. In 1986 only 37 thrombophilia profiles were performed. By 1993 this number was 600. Undoubtedly it was the discovery of APC resistance and the factor V Leiden mutation in the mid-1990s that elevated the profile of thrombophilia testing to such a degree that it became commonplace with 2,300 thrombophilia profiles (phenotypic measurement of natural anticoagulant levels and genetic analysis of gain-of-function polymorphisms) performed in Cambridge in 1995 and 3,500

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in 1999. This practice undoubtedly arose as a response to association studies. In consecutive patients presenting with a first venous thrombosis approximately 5% will have deficiency of a natural anticoagulant by phenotypic testing, 15% will have the factor V Leiden mutation and 3-5% the factor II Leiden (F2G20210A) mutation. Compared to the incidence of these defects in control groups odds ratios can be calculated as an estimate of relative risk of thrombosis. Odds ratios for a first thrombotic event in association with protein C or S deficiency are approximately 10, with antithrombin deficiency 20, with the factor V Leiden mutation 4 and with the prothrombin gene mutation 2 [5]. Furthermore, in highly selected thrombosis-prone families there is no doubt that the risk of thrombosis is significantly higher in affected family members compared to those family members without the identifiable thrombophilic defect. It is therefore easy to appreciate why the concept of testing for heritable thrombophilia was thought by some experts to be likely to have clinical utility. It was presumed that when a patient presents with venous thrombosis identification in the laboratory of a thrombophilic defect, which is clearly a risk factor for thrombosis, might indicate a high risk of recurrence in the index patient. Similarly, identifying the same defect in family members would identify those at high risk and therefore allow avoidance of high risk situations or facilitate targeted prophylaxis at times of unavoidable high risk [2]. However, the clinical utility of thrombophilia testing requires closer evaluation.

How do the Results of Laboratory Tests Affect Treatment of Symptomatic Patients?

There is currently no evidence that thrombophilia testing should influence the intensity of heparin therapy, the oral anticoagulant loading schedule, the intensity of oral anticoagulation or the duration of anticoagulation in affected symptomatic patients [1,6,7]. Whilst there are family studies and small series indicating a high frequency of recurrence in patients with heritable thrombophilia more direct comparisons between patients and families with and without thrombophilic defects are required.

Comparisons have been made for patients with and without the factor V Leiden and F2G20210A polymorphisms. Almost all studies indicate that heterozygosity for these polymorphisms does not predict a greater risk of recurrence after stopping oral anticoagulant treatment [8-16]. A single small study, which included 11 patients homozygous for the factor V Leiden mutation, suggested a 4-fold increased risk of recurrence compared to heterozygotes and patients without the mutation [11]. However, the inter-patient risk varied considerably. Further studies are required to clarify the ben-

efit and risk of prolonged anticoagulation in homozygous patients. Similarly, patients with combined defects may be at increased risk of recurrence [13], but this must be confirmed, or refuted, in future studies.

Retrospective studies, documenting historical thrombotic events, have reported high recurrence rates in patients with natural anticoagulant deficiency [17]. However, a major source of bias with such studies is that patients with recurrent venous thromboembolism are more likely to be investigated leading to an overestimate of risk.

The most accurate measurement of recurrence risk is from prospective follow up of patients recruited from a cohort of consecutive patients diagnosed with a first episode of venous thromboembolism. The prospective Cambridge Venous Thromboembolism Study (CVTE) recruited consecutive patients with venous thromboembolism. The first results published in 2003 showed that thrombophilia testing had no predictive value for recurrence in the proband [15]. This study was powered to detect a 10% difference in recurrence of thrombosis at two years between patients with and without laboratory evidence of thrombophilia. The risk of recurrence in relation to presence or absence of thrombophilia was not significantly different. In contrast the risk of recurrence in relation to the clinical circumstances at the time of the first event was highly statistically significant. It can be concluded that clinical circumstances have a significantly higher predictive value than thrombophilia testing. The findings from long-term follow up of the Leiden Thrombophilia Study (LETS) are similar [16]. Hazard ratios were calculated for recurrent thrombosis according to individual thrombophilia defect. No defect was associated with a significant hazard ratio leading the authors to conclude 'prothrombotic abnormalities did not play an important role in determining risk of recurrence'.

Case Finding

The next issue is whether screening asymptomatic relatives of patients with thrombosis has clinical utility. In this regard it is important to distinguish testing from screening. Testing is performed in the presence of symptoms or signs of a particular disease whilst screening is performed in the absence of disease. Testing or screening equates to genetic counseling, which is defined as the effective communication and provision of information to an individual or family concerning the diagnosis of, or risk of, inheriting a genetic disease. Central to this issue is the concept of clinical utility. Clinical utility is the likelihood that a test will lead to an improved health outcome. In the case of thrombophilia testing we have to ask if it is likely that thrombophilia testing will lead to an improved health outcome and if it is likely is

it worth the cost, not only in terms of the financial cost of laboratory testing and clinician time but the psychosocial cost of identifying a genetic trait with a low penetrance for a late onset genetic disease in a large number of individuals?

The issue has been addressed objectively by a number of studies. Middeldorp and colleagues performed a prospective outcome study in 470 asymptomatic carriers of the factor V Leiden mutation. Carriers were identified by screening first degree relatives of 247 symptomatic probands in three centres in the Netherlands. The total annual incidence of venous thromboembolism was 0.58% with an incidence of spontaneous events of only 0.26%. This led the authors to conclude that the absolute annual incidence of spontaneous venous thromboembolism in asymptomatic carriers of the factor V Leiden mutation is low and does not justify routine screening of the families of symptomatic patients. Simioni and colleagues in Padua similarly found that the total annual risk of venous thromboembolism in 313 asymptomatic carriers of the factor V Leiden mutation, related to 131 symptomatic probands, was 0.67% with a risk of spontaneous venous thromboembolism of only 0.17%.

The predictive value may be greater for deficiency of a natural anticoagulant. A multicentre study conducted in centres in Italy, the Netherlands and Canada prospectively assessed the incidence of venous thromboembolism in non-treated asymptomatic affected relatives of symptomatic probands [18]. The annual incidence of all venous thrombotic events was 1.5% for all deficiencies combined (antithrombin, protein C, protein S) with an annual incidence of spontaneous events of 0.8%.

So Who to Test?

When considering who to test for evidence of heritable thrombophilia testing is only appropriate in the presence of a family history, particularly the presence of a history of familial idiopathic venous thrombosis. The next consideration is whether to test for common gain of function mutations which are associated with only a relatively low risk but for which test accuracy is reliable. The answer appears to be not to test for these common mutations as there is prospective study data indicating low clinical utility in both relatives [19,20] and probands [8-16]. The third consideration is whether to test for uncommon deficiencies associated with a relatively high risk, namely antithrombin and protein C deficiency. However, test accuracy is less reliable [21]. If case finding is to be undertaken accuracy and predictive value would be greatly increased by direct mutation analysis. This is not only because of the inaccuracy of phenotypic testing but the very variable and diverse thrombotic risk associated with different mutations.

Proposed Testing Strategy

When a patient presents with venous thromboembolism the first question from the perspective of thrombophilia testing is whether or not there is a family history. If there is no family history then the clinical circumstances associated with the thrombotic event need considering. If the thrombosis was precipitated by surgery or cancer then no thrombophilia tests are indicated. If the thrombosis was not precipitated by surgery or cancer then testing for acquired antiphospholipid activity might be performed depending on the nature of the precipitating trigger at the time of the thrombotic event. Anticoagulation might be continued in patients with positive results and a minimal trigger for the thrombotic event. However, if there is a family history of venous thromboembolism then testing for heritable thrombophilia might be considered, accepting that at present there is no strict definition of what constitutes a positive family history. As testing for common low risk gain-of-function polymorphisms has little or no clinical utility there is no need to test for factor V Leiden or prothrombin gene mutations. Testing for antithrombin and protein C activity could be performed. If levels are persistently low then other symptomatic family members could be tested phenotypically but ideally specific mutation analysis could be instituted. Once the mutation was identified a family study with case-finding could be initiated. If there was strong co-segregation between the mutation and thrombosis then appropriate advice could be given to affected family members regarding risk avoidance and use of thromboprophylaxis at times of unavoidable high risk, such as surgery. If there was discordance between the mutation and the clinical phenotype then all family members should be given similar advice regarding risk avoidance and use of thromboprophylaxis at times of unavoidable high risk. The clinical utility of testing for protein S deficiency is even less clear.

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