Genetic hypercoagulability: prevention suggests testing family members

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Dahlback in 1993 and Bertina in 1994 made the landmark discovery that resistance to activated protein C due to a point mutation in the factor V gene (G1691A in exon 10, leading to Arg506Gln) is associated with a 6- to 8-fold increased risk of venous thrombosis. The importance of these findings, which have since been confirmed and cited more than 2000 times in the medical literature, is due to the fact that heterozygosity for factor V Arg506Gln (generally known as factor V Leiden) is present in approximately 20% of unselected patients who present with a first episode of venous thrombosis and, most important, in approximately 4% of general white populations. Another piece of evidence supporting the importance of genetic risk factors in causing venous thrombosis was added in 1996, when again Bertina and his colleagues found that the prothrombin G20210A polymorphism has a frequency of 6% in patients with a first episode of venous thrombosis, contrasting with approximately 2% in the general white population. Adding to factor V Leiden and prothrombin G20210A the rarer deficiencies of the naturally occurring anticoagulant proteins antithrombin, protein C, and protein S, the proportion of venous thromboses attributable to genetic factors is 25% to 30%, at least as large as that attributable to well-established acquired risk factors such as surgery, trauma, prolonged immobilization in bed (more than 7 days), pregnancy and puerperium, estrogen use, and cancer.

With these genetic risk factors of venous thrombosis having such a weight and prevalence in the general population, the first obvious question is whether they should be looked for in healthy individuals with no personal or family history of thrombosis, particularly when they are exposed to acquired factors that may interact with genetic factors to increase the risk of venous thrombosis. The magnitude of the interaction between genetic and acquired factors can be exemplified by one of the most frequently occurring genetic thrombophilic abnormalities: factor V Leiden and oral contraceptive intake. By analogy, the same negative consideration applies to pregnant women and to individuals of both sexes exposed to major surgery, immobilization, cancer, and hormone replacement therapy, because there is no evidence that the interaction among these risk factors and heterozygosity for factor V Leiden is more thrombogenic than that between the latter and oral contraceptive intake.

A special situation is that of asymptomatic relatives of index patients with a thrombophilic defect diagnosed after an episode of venous thrombosis. In these individuals, screening is obviously more focused and potentially more fruitful than in the general population because all the genetic risk factors are transmitted as autosomal dominant traits. The first issue is whether the results of screening would be advantageous for family members.

In principle, screening entails the possibility of giving advice for antithrombotic prophylaxis to these individuals. There is no evidence that their lifelong risk of thrombosis justifies exposure to the risks associated with primary prophylaxis with oral anticoagulants, because many individuals with a genetic thrombophilic abnormality never develop thrombotic symptoms, nor do these defects increase mortality. However, when asymptomatic thrombophilic individuals are exposed to acquired risk factors, the increased risk of thrombosis might in principle be reduced with relatively little risk and cost by adopting short-term prophylaxis with low-dose unfractionated or low-molecular-weight heparin.

What is the evidence in favor of this diagnostic strategy and of the ensuing prophylaxis strategy? In a retrospective study conducted in Italy in 1994, 238 patients with antithrombin, protein C deficiency, or protein S deficiency were analyzed for the incidence of thrombotic events prediagnosis and postdiagnosis of the thrombophilic abnormality. In the prediagnosis period, antithrombotic prophylaxis was not implemented at the time of exposure to acquired thrombosis risk factors. However, after diagnosis, short-term prophylaxis with heparin was usually implemented. This approach reduced the incidence of both first (0.7/100 patient-years postdiagnosis vs 1.7 prediagnosis) and recurrent (1.3/100 vs 4.8/100 patient-years) thrombotic episodes. Among the limitations of this study are its retrospective design and the fact that factor V Leiden and prothrombin G20210A were not known as risk factors at the time of the study and so they were not considered in the analysis.

Another piece of evidence in favor of the usefulness of screening and of antithrombotic prophylaxis during risk periods stems from a prospective cohort study carried out in Europe and Canada in 208 affected but asymptomatic family members of 94 symptomatic antithrombin, protein C–, and protein S–deficient patients who had a venous thrombotic event. During 40 periods of exposure of these individuals to acquired risk factors, the decision to use antithrombotic prophylaxis and the regimens used were left to the choice of the treating physicians. The incidence of risk period–related, objectively documented, first venous thromboembolic episodes was 4.5% in the individuals who received prophylaxis, as compared with 16.7% in those who did not receive prophylaxis. Limitations of this study are the very small number of
periods of exposure to transient risk factors, the nonuniform and nonrandom approach to antithrombotic prophylaxis, and, as for the retrospective Italian study, the fact that the factor V and prothrombin mutations were not known when the study was carried out. These genetic risk factors carry a smaller risk of thromboembolism than antithrombin, protein C deficiency, and protein S deficiency.\textsuperscript{12,13}

We recognize that several arguments can be made against the adoption of screening and prophylaxis in members of thrombophilic families. The cost of screening, particularly of DNA testing, is not negligible and cost effectiveness remains to be demonstrated. There is also the risk of labeling individuals with a genetic “disease” who in many instances will never have thrombotic disease. Besides generating anxiety, this situation might create problems in obtaining insurance in some schemes of health care delivery, particularly in the United States. These limits notwithstanding, we advise thrombophilia screening in asymptomatic relatives of symptomatic patients carrying genetic abnormalities such as factor V Leiden, prothrombin G20210A, antithrombin, protein C deficiency, or protein S deficiency. When women found to carry one of these abnormalities consider taking oral contraceptives, we try to give them a balanced view of the absolute and relative risk of thrombosis associated with the drug use, taking into account the age of the woman and her general health condition. The same approach is adopted for women who consider hormone replacement therapy, informing them that the background annual incidence of venous thrombosis at their age is higher than that in women of childbearing age (between 1 in 1000 and 1 in 5000). When men and women with thrombophilic abnormalities, even if asymptomatic, undergo procedures of major surgery, we advise the same regimen of short-term antithrombotic prophylaxis with low-dose unfractionated or low-molecular-weight heparin that is routine for all individuals older than 40 years of age.

We recognize that this diagnostic and prophylactic approach is not supported by evidence stemming from prospective clinical studies, but the corresponding risks and costs are considered acceptable in a country that, like Italy, traditionally has a system of health care delivery focused on prevention. In the United Kingdom, a country with a similar system, Greaves and Baglin\textsuperscript{14} think that suitable studies should first demonstrate that the expenses and risks involved in screening and prophylaxis are justified by improved patient care. We appreciate their position, but because such studies would require extremely large sample sizes to be definitive, we doubt they will ever be undertaken, or if begun, we will have to consider the issues of hypercoagulability in asymptomatic family members of thrombophilic patients for a considerable time until the studies are completed.

References


