Problems related to counseling in genetic thrombophilias

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Key Words

Genetic Thrombophilias; Factor V Leiden; Antithrombin deficiency; Protein C deficiency; Protein S deficiency

Abstract

Venous Thrombosis is a major cause of mortality and morbidity in Western populations and in 30% of cases is associated to genetic susceptibility. Ideally, the identification of carriers of such susceptibility, known as thrombophilia, may allow for predicting the likelihood of recurrence in symptomatic patients and the risk of thrombosis in their relatives, leading to tailored plans of therapy and prophylaxis. In practice, this is greatly complicated by the high heterogeneity of both genotype and phenotype of inherited thrombophilia and by the lack of evidence-based guidelines for managing carriers. These issues and their impact on the process of genetic counseling for individuals suspected to have an inherited thrombophilia are discussed.

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Background

The annual incidence of Venous Thrombosis (VT), a major cause of mortality and morbidity, is about 1 per 1000 in Western populations. Among patients diagnosed with VT, more than 30% carry a genetic susceptibility to the disease. Familial tendency to thromboembolic disease has been known for half a century, and since 1965 several genetic alterations underlying thrombophilias has been described. Identification of carriers of inherited thrombophilia would ideally allow to predict the risk of VT, therefore leading to optimizing decisions on prophylaxis and therapy. In practice, this task is complicated by the complexity of genetic susceptibility to VT, which is characterized by extremely heterogeneous genotype and phenotype. For this reason, identification of carriers should be pursued exclusively through a comprehensive process of genetic counseling. The steps of the process are here described and related issues are discussed.

Identification of putative carriers of inherited thrombophilias

Even though 34% of unselected patients with VT are estimated to carry an inherited thrombophilia, the fraction rises to 70% when additional factors are present [1]. These factors are: an early age at VT diagnosis (with a cut-off varying from 40, to 45, to 50 years in different studies), a family history of VT, multiple events in the same patient and the absence of acquired

risk factors (except for pregnancy or oral contraceptives). Nevertheless, although increasing the probabilities of a genetic defect leading to thrombophilia, these criteria are not consistently met in individuals with an inherited susceptibility to VT. For instance, in contrast with most hereditary disorders, family history has been reported to be of limited value for detecting carriers of genetic thrombophilias [2,3], so that a significant number of at-risk individuals could be missed if the only criterion of family history was used for selection. Nevertheless, this could also be due to a low accuracy of reported family history, which underlines the importance of collecting an extended pedigree and of verifying the clinical history of family members to increase the reliability of pedigree analysis.

Testing for inherited thrombophilia and interpreting the result

Genetic defects leading to thrombophilia include mutations that result in a loss of function in the encoded protein and mutations that, conversely, result in a gain of function. Both the types of mutation lead to a failure in the balance between pro-coagulating and anti-coagulating factors which results in increased generation or decreased neutralization of thrombin. The most important genetic variants responsible for inherited thrombophilia are reported in table 1, and mechanisms of coagulation affected by these mutations are shown in figure 1. In addition to these, other genes are rarely involved in inherited thrombophilia. Among those, there are plasminogen, genes involved in homocysteine metabolism, mutations of which lead to hyperhomocystinemia (for instance homozygous homocystinuria due to cystathionine- β -synthase deficiency, and homozygous C677T mutation in the methylenetetrahydrofolate reductase), and genes the mutations of which lead to dysfibrinogenemia, increased levels of factor VIII, factor IX, factor XI, fibrinogen.

Pre-test counseling regards medical and psychological risks and benefit and limitations of testing and has the aim of enabling patients to give their informed consent to the analysis.

Post-test counseling should help people to make decisions on their own life and on their medical management based on test results. In this view, assessing the risk associated with a specific genetic defect is crucial. This is however complicated by the high variability in the penetrance of the involved genes. In fact, the risk of VT associated with Factor V Leiden is 13 to 25%, and that associated with one among deficiency of protein C, of protein S, or of antithrombin is 19 to 57%. Nevertheless, as these variants are common in white populations, coinheritance of more than one predisposing defect is a relatively probable event, which points out the need for a comprehensive genetic testing in order to perform a really accurate risk

assessment. The combination of Factor V Leiden and deficiency of either protein C, or protein S, or antithrombin leads to a risk of 72-93%. Similar interactions have been reported for coinheritance of Factor V Leiden and the mutation G20210A in the prothrombin gene, and an increased risk has also been demonstrated for homozygosity of each of these variants. Clearly, an individual whose risk is estimated around 13% and one whose risk is assessed as high as 93% should be managed differently. Nevertheless, the genetic heterogeneity of thrombophilia hampers the accuracy of individual risk assessment. In fact, a negative result is very difficult to interpret, as changes in genes other than those analyzed can have occurred. Similarly, when a single defect is detected, the coinheritance of additional, rare predisposing defect, which would change the risk, cannot be excluded.

Options for prevention and treatment

More than half of thromboembolic events in susceptible individuals are provoked by additional risk factors; recognizing hereditary thrombophilia may therefore theoretically lead to avoiding such factors or to accompanying them with prophylaxis. On the other side, it should be considered that, if VT is associated with significant mortality, anticoagulant treatment is potentially dangerous as well, with a 1% annual risk of major haemorrhage.

Generally, risk factors are those situations that increase blood coagulability or make the blood flow slowly, such as advanced age, major surgery, prolonged immobilization, malignancies, pregnancy and estrogen use. Genetic counseling is most likely to deal with the latter two situations, that are therefore more extensively described.

Pregnancy – Up to 60% of women with an antithrombin deficiency and up to 20% of women with a deficiency of either

Fig. 1. Mechanisms of coagulation control affected in inherited thrombophilias.

Table 1. Major genetic variants associated with inherited thrombophilia

Gene	Chromosome	Variant	Protein change	Effect	Frequency in Western populations (%)	
					VT patients	Healthy subjects
Factor V	1p23	G1691A (Factor V Leiden)	Arg506Gln	Impaired inactivation of Factor Va Diminished cofactor activity in inactivation of factor VIIIa by protein C	20	4.8
Prothrombin	11p11-12	G20210A	None (untranslated region)	Increased level of plasma Prothrombin	6-19	2-15
Protein C	2q13-q14	161 different mutations		Decreased level of plasma Protein C	3-4	0.2-0.4
Protein S	3p11.1-q11.2	131 different mutations		Decreased level of plasma Protein S	2-3	unknown
Antithrombin	1q23-q25	127 different mutations		Decreased activity of Antithrombin	1-2	0.02

protein C or protein S experience VT during pregnancy and the puerperium [4], with a relative risk for asymptomatic women with one of those defects as high as 8 [5]. Nevertheless, the most common cause of primary and recurrent VT in pregnancy is factor V Leiden, which is associated with a relative risk between 5 and 16 [6]. An increased risk is also associated with the G20210A mutation in the prothrombin gene, the coinheritance of which with factor V Leiden further increases the risk. In addition, inherited thrombophilia increases the risk for other complications of pregnancy like fetal loss, hypertensive disorders, placental abruption and intrauterine growth restriction.

Although screening for thrombophilia is recommended in women with known risk factors (personal or family history of VT, early-onset, previous pregnancy complications possibly related to inherited thrombophilia), management of carriers is still matter of debate. Nevertheless, recent expert opinion suggests that prophylactic heparin should be administered even in asymptomatic carriers, with higher (therapeutic) doses being recommended in women with severe thromboembolic events in previous pregnancies and in those at high genetic risk (homozygous Factor V Leiden or combined defects) [7, 8]. Counseling women about pregnancy is a very delicate process, because it can affect decisions on issues extremely important for their lives like childbearing. Nevertheless, every thrombophilic woman who intends to become pregnant, preferably together with her partner, should be properly informed about risks of both pregnancy and anticoagulant prophylaxis. Once aware of these issues, they should be helped to analyze their fears and desires and to reach a decision thanks to a multidisciplinary approach (including sessions with a psychologist and with every physician possibly involved in the woman's management).

Estrogen use - The use of oral contraceptives is recognized to increase the risk of VT in all women, but in carriers of an inherited thrombophilia the risk is much higher. Women heterozygous for factor V Leiden have been reported to have a rel-

ative risk of 34.7, compared to 3.8 in non-carriers, with the risk associated with third-generation contraceptives being twice that associated with second-generation contraceptives. This raises the issue of whether to test for thrombophilia all women willing to start oral contraceptives. It has been estimated that, if the prevalence of defect like factor V Leiden was 10%, 200000 women should be screened to prevent one death for pulmonary embolism [9]. Such screening is therefore considered not cost-effective and genetic testing is exclusively recommended for those women who have a higher probability to carry an inherited thrombophilia, such as those with a personal and or family history of VT. Nevertheless, as previously stated, this may lead to underestimating the risk of women who actually carry a mutation without having such a history.

Hormone-replacement therapy in healthy, post-menopausal women increases the risk of VT by a factor of two to four; the risk is, again, significantly increased in carriers of thrombophilic defects [10]. Nevertheless, due to the widespread use of hormone-replacement therapy, it is not advisable to screen all women before starting the treatment.

In any case, women with known thrombophilia should be counseled against taking estrogens for either contraception or hormone replacement, as this may trigger thromboembolic events.

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