Heritable Thrombophilia

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Abstract

Venous thromboembolism (VTE) is a common source of morbidity and mortality in developed countries. Heritable risk factors (thrombophilia) for VTE can be identified in 30–50% of affected patients. Factor V Leiden, prothrombin 20210G>A, and deficiencies of antithrombin, protein C and protein S increase the risk of a first VTE. However, an individual’s thrombotic risk is determined by a complex interplay of genetic, acquired and circumstantial risk factors. Thrombophilia screening should only be ordered in a highly selected patient group, such as in patients with strong family history of recurrent unprovoked VTEs. Testing for heritable thrombophilia involves a range of complex coagulation-based tests along with genetic testing, testing is expensive, and the results can be affected by preanalytical variables. Current treatment for thrombophilia involves both prophylaxis with low-molecular-weight heparin and treatment involving heparin, warfarin or purified factor concentrate. Aim of the study is to spotlight on causes of inherited thrombophilia, screening and diagnosis.

Keywords: Antithrombin, Factor V Leiden, Protein C, Protein S, Prothrombin 20210G>A, Thrombophilia.

1. Introduction

Hemostasis is a complex system that includes the participation of several factors: blood vessel endothelium, platelets, blood coagulation factors, fibrinolytic process and coagulation inhibitors [1]. The coagulation process that leads to haemostasis involves a complex set of protease reactions. These reactions convert fibrinogen, a soluble protein, to insoluble strands of fibrin, which, together with platelets, form a stable thrombus. Several coagulation cascades models have been proposed, including the intrinsic and extrinsic pathway model and the more recent cell-based model [2]. Regulation of coagulation is exerted at multiple levels, either by enzyme inhibition or by modulation of the activity of the cofactors. Antithrombin, protein C and protein S are the most important regulators of coagulation. Together with tissue factor pathway inhibitor (TFPI) and the fibrinolytic system, they constitute the main natural anticoagulants and antithrombotic mechanisms (figure:1) [3]. Thrombophilia can be defined as a predisposition to form clots inappropriately. These blood clots can cause problems such as deep vein
Thrombotic events during infancy and childhood are increasingly recognized as a significant source of mortality and morbidity. The predisposition to form clots can arise from genetic factors, acquired changes in the clotting mechanism, or, more commonly, an interaction between genetic and acquired factors. 

In clinical practice the heritable factors predisposing to venous thrombosis that are most widely assessed are: gain of function genetic polymorphisms e.g. [factor V Leiden (FVL) and the prothrombin gene mutation (PGM)] and loss of function mutations as in genetic deficiencies of the naturally occurring anticoagulants [antithrombin (AT), protein C (PC), and protein S (PS)] [7].

2. Factor V Leiden

Factor V Leiden thrombophilia is the most common form of inherited thrombophilia which is a genetic disorder characterized by a poor anticoagulant response to activated protein C (APC) and an increased risk for VTE.[8] Factor V Leiden arises from the specific replacement of guanine by adenine at nucleotide 1691 in the gene for factor V, determining the replacement of arginine by glutamine at the APC-cleavage site. As a result of this single amino acid substitution, factor Va becomes resistant to APC, and its inactivation is ten times lower than normal. As a result, more factor Va is available within the prothrombinase complex, increasing coagulation by increased generation of thrombin.[9]

The relative risk of venous thrombosis is increased approximately 4- to 8-fold in individuals who are heterozygous for the FV Leiden mutation and up to 80-fold in individuals who are homozygous.[8] Factor V also has other polymorphisms cooperated with FVL, increases the impact of activated protein C resistance (APC-R) and risk of venous thrombembolism (VTE) such as pseudo-homozygous factor V Leiden, factor V gene haplotype (HR2), factor V Liverpool, factor V Cambridge, factor V Hong Kong, factor V Nara and factor V Bonna [10]. The functional assay for APC-R is the preferred initial test, which if abnormal can be followed up with the DNA based assay to confirm FVL genotype [11].

3. Prothrombin Gene Mutation

The prothrombin gene mutation is the second most commonly identified cause of heritable thrombophilia. It is an autosomal dominant mutation that results from a single missense mutation (guanine to adenine; G→A) at nucleotide position 20210, which is present in the 3' untranslated region of the prothrombin gene. The mutation alters mRNA formation
by affecting 3’ end processing and/or enhancing translation efficiency, resulting in a “gain of function” of the prothrombin gene, that leads to increased plasma prothrombin levels [12]. This mutation is associated with a two-to-four-fold increased risk of VTE throughout life. Prothrombin levels are increased by about 30% in heterozygotes and 70% in homozygotes [13]. As factor Va, bound in the prothrombin-factor Va complex, is resistant to APC cleavage, increased levels of prothrombin increase the half-life of factor Va leading to a hypercoagulable state [14]. Heterozygous individuals show a 3-fold increase in the risk of venous thrombosis, however homozygous individuals appear to have greater predisposition to develop early idiopathic recurrent VTE than heterozygotes [9]. Molecular testing methods are essential for the accurate diagnosis of FII G20210A mutation [11].

Table 1: The different risk factors for venous thrombosis [6].

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Inherited</th>
<th>Mixed or unknown</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>Antithrombin deficiency</td>
<td>Hyperhomocysteinemia</td>
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<tr>
<td>Previous thrombosis</td>
<td>PCd</td>
<td>High levels of factor VIII</td>
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<td>Immobilization</td>
<td>PSd</td>
<td>APC-resistance in the absence of Factor V Leiden</td>
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<td>Major surgery</td>
<td>Factor V Leiden mutation</td>
<td>High levels of factor IX</td>
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<tr>
<td>Orthopedic surgery</td>
<td>Prothrombin G20210A mutation</td>
<td>High levels of factor XI</td>
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<tr>
<td>Malignancy</td>
<td>Dysfibrinogenemia</td>
<td>High levels of TAFI</td>
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<tr>
<td>Oral contraceptives</td>
<td></td>
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<tr>
<td>Hormonal replacement therapy</td>
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<td>APS Essential thrombocythemia</td>
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<tr>
<td>Polycythemia vera</td>
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<td>Paroxysmal nocturnal hemoglobinuria</td>
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<td>Splenectomy</td>
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TAFI = Thrombin activated fibrinolysis inhibitor, APC = Activated protein C, APS = Antiphospholipid antibody syndrome, PCd = Protein C deficiency, PSd = Protein S deficiency
4. Protein C Deficiency

Protein C, a vitamin K-dependent glycoprotein, is a serine protease precursor with anticoagulation inhibiting action of FVα and FVIIIα by proteolytic action [15]. Protein C deficiency (PCD) can be an autosomal dominant or recessive disease. Patients with PCD may have type I (quantitative deficiency) or type II (qualitative abnormality) disease. Most patients are heterozygotes with ∼50% of normal protein C levels. There appears to be no difference in clinical expression of phenotype (thrombosis) between the Type I and Type II defects of PC [16]. Heterozygous individuals have an approximately 7-fold increased risk of venous thrombosis compared with normal individuals. Warfarin-induced skin necrosis is an unusual syndrome seen in certain patients with heterozygote PCD. Neonatal purpura fulminans is seen in homozygous newborns of heterozygous parents [17]. Protein C chromogenic assays are the preferred initial test, given their better performance characteristic. If the result is low, an antigenic PC assay is performed to determine whether the protein C defect is quantitative (type I) or qualitative (type II) [18].

5. Protein S Deficiency

Protein S is a vitamin K-dependent glycoprotein synthesized in the liver. It is an important cofactor for APC anticoagulant pathway and TFPI [19]. Hereditary PS deficiency is transmitted in an autosomal dominant fashion. As described for PCD. Patients with protein S deficiency may have quantitative or qualitative disorders [20]. Venous thrombosis develops in 60–80% of patients who are heterozygous for PS deficiency. The remaining patients are asymptomatic, and some heterozygous individuals never develop VTE [21]. Homozygous patients typically present in newborns with purpura fulminans [22]. Protein S antigen assays are the preferred initial assays, given the variable performance characteristics of the functional assays [23].

6. Antithrombin Deficiency

Antithrombin is the natural inhibitor of thrombin and FXa. Congenital AT deficiency is an autosomal dominant genetic disease, which is the strongest risk factor of venous thrombosis [24]. Patients with AT deficiency may have either type I (quantitative deficiency) or type II (qualitative abnormality) disease. Type II deficiency is further divided into three subgroups: mutations affecting the reactive site (type IIRS), mutations at the heparin binding site (type IIHBS) and pleiotropic effect defects (type IIPE) [25]. Most patients with hereditary AT deficiency are heterozygous, since homozygous variants [except for heparin binding site (HBS) mutations] are thought to be incompatible with life [26]. Functional assays for AT are generally chromogenic assays and are based on inhibition of factor IIa (thrombin) or factor Xa; antigenic assays for AT are generally based on immuno-turbidimetric methods [27]. It is possible for more than one thrombophilic tendency to be inherited. This is most commonly seen in people who are heterozygous for both factor V Leiden and the prothrombin gene mutation. Although such people may have a higher risk of VTE than those who are heterozygous for one gene only, some studies found the risk to be similar to that of factor V Leiden alone [28].

7. Thrombophilia Screening

Thrombophilia screen is a highly specialized test which requires careful consideration of the patient’s clinical history, treatment choices and preferences, and should not be used in unselected group of patients who present with an episode of acute VTEs [29]. There are situations, or
conditions in which thrombophilia testing is advisable according to the British Committee for Standards in Hematology (BCSH) guidelines. These are idiopathic (unprovoked) VTE, especially below the age of 50 years, thrombosis in unusual sites, skin necrosis following the anticoagulant treatment, neonatal purpura fulminans, recurrent VTE, first VTE with strong positive family history, asymptomatic family members of relatives having severe inherited thrombophilia, pregnancy complications or in women taking contraceptive pills, or under hormonal replacement therapy [30]. Testing for thrombophilia during the acute phase of a thrombotic event should be avoided as several factors may influence test results acutely and the presence of a heritable thrombophilia does not affect the initial management of VTE. The background medical condition of patients can affect coagulation tests. Also, knowledge of which drugs are being taken at the time of testing is important. Interpretation of results can be challenging and often requires expertise in conjunction with relevant clinical details [11]. The “thrombophilia screen” for heritable disorders that clinicians request usually involves measurement of antithrombin, protein C, and protein S levels, and testing for the factor V Leiden and prothrombin gene mutations. This panel is completed by the laboratory investigations for Anti phospholipid syndrome. It is advisable to perform the screening tests of coagulation (i.e., prothrombin time, activated partial thromboplastin time, thrombin time) to detect the presence of different anticoagulant drugs, which may interfere with certain laboratory tests. Thrombin time is also useful to screen for fibrinogen abnormalities, like dysfibrinogenemia. Some authors also recommend testing for elevated FVIII and for APC resistance not due to FVL. Thrombophilia testing should be completed by measurement of plasma homocysteine and blood typing [5].

8. Thrombophilia Treatment

Current treatment for thrombophilia involves both prophylaxis with low-molecular-weight heparin and treatment involving heparin, warfarin or purified factor concentrate. Asymptomatic patients should not be treated but should be considered for prophylaxis when they experience high-risk procedures such as surgery [5]. As the antithrombotic effect of warfarin necessitates the inhibition of factor II, which has a very long half-life (60-72 h) as compared to other factors (6-24 h), it takes approximately 6 days for warfarin to exert its full efficacy even though the earliest changes in the international normalized ratio (INR) can be seen after 24 to 36 h. The average number of days to achieve therapeutic INR (2 to 3) after starting warfarin is reported to be 5-6 days. To counter that, heparin ‘bridging’ is recommended for a minimum of 5 days and until the INR is 2.0 or above for at least 24 h [31]. Infants with neonatal purpura fulminans should be treated with PC replacement therapy [32]. Some AT-deficient patients may experience heparin resistance, requiring the administration of AT. Supplemental AT may make it easier to achieve therapeutic anticoagulation with heparin in these patients [33].

9. Thrombophilia Prophylaxis

Although maintaining INR of 2 to 3 with oral anticoagulation therapy seems highly effective in preventing thrombotic recurrences, this benefit is partially offset by the risk of major bleeding. Short-term prophylaxis has been recommended during high-risk situations, especially in homozygous patients. However, a decision to prolong the duration of the anticoagulation therapy must be tailored to the individual patient's risk of recurrent thrombosis in the absence of treatment and to the risk of bleeding [5].
10. Conclusion

Thrombophilia is a risk factor for many diseases such as deep vein thrombosis and pulmonary embolism. Thrombophilia may be hereditary or acquired. The most common cause of hereditary thrombophilia is factor V Leiden, and the second most common cause is prothrombin G20210A gene mutation. Thrombophilia screening should be done in certain circumstances such as idiopathic (unprovoked) VTE, especially below the age of 50 years, thrombosis in unusual sites and skin necrosis following the anticoagulant treatment. Thrombophilia prophylaxis with low-molecular-weight heparin has been recommended during high-risk situations, especially in homozygous patients.

References


