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Familial thrombophilia: genetic risk factors and management

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Abstract. There are now a number of potential candidates for inherited thrombophilia but a definite causal relationship has been established for only a proportion of these. Accepted causes of familial thrombophilia include the factor V Leiden defect and the prothrombin 20210 G>A variant, as well as deficiencies of antithrombin, protein C and protein S. Together these inherited abnormalities account for 30–50% of individuals presenting with venous thromboembolism. Factor V Leiden, which is present in up to 7% of the European population, is the most common cause of familial thrombophilia. On a worldwide basis its prevalence varies greatly with ethnic origin. In common with other types of familial thrombophilia the frequency of factor V Leiden is highly dependent on the population group studied. Venous thromboembolism, present in approximately 55% of individuals with familial coagulation inhibitor deficiencies, is the predominant clinical manifestation of familial thrombophilia. There are indications that the venous thrombotic risk is somewhat less in those with factor V Leiden. The thrombotic risk is markedly increased in those with combined defects and in those who are homozygous for factor V Leiden. Risk factors for thrombosis include pregnancy, including the puerperium, surgery, oral contraceptive usage and prolonged periods of immobilization. A substantial proportion of venous thrombotic events may occur spontaneously, i.e. without an obvious precipitating event. The management of patients with familial thrombophilia comprises counselling, thromboprophylaxis and thrombosis treatment. Although the immediate treatment of an acute thrombotic event is not significantly different from that of patients without recognised abnormalities, detailed patient management is seriously hampered by a lack of appropriate clinical trials. Prospective clinical studies, designed to ascertain individual thrombotic risk and to evaluate different therapeutic strategies are urgently required.

Keywords: thrombophilia, venous thrombosis, risk factors, management.

Introduction

The coagulation system is essentially a series of linked reactions involving zymogens, their respective serine proteases and cofactors. The system is controlled through a series of feedback mechanisms and by the action of inhibitors. The functions of the coagulation system are closely linked to those of the fibrinolytic system with fibrin being the natural substrate for the fibrinolytic enzyme, plasmin.

It is only in recent years that the physiological and clinical importance of blood coagulation inhibitors has become appreciated. Although antithrombin III deficiency was first described in 1965, it was not until the 1980s, following the first reports of familial deficiencies of protein C and protein S that coagulation inhibitors became generally recognized as being at least as important as procoagulants in the pathogenesis of venous thromboembolism.

Thrombophilia is defined as an increased tendency to thrombosis and can be inherited or acquired (Table 1). The thrombotic events in patients with inherited thrombophilia tend to occur at a young age, are often idiopathic, recurrent, follow minimal provocation (e.g. aeroplane flight) and tend to occur at unusual sites (e.g. inferior vena cava, mesenteric and cerebral veins).

Venous thrombosis

Venous thromboembolism is the predominant clinical manifestation of familial thrombophilia. This usually manifests as deep vein thrombosis or pulmonary embolism but venous thrombosis in unusual sites is

Table 1 Risk factors for venous thrombosis

Acquired	
	Age
	Previous thrombosis
	Surgery
	Obesity
	Immobility
	Sepsis
	Malignancy
	Oral contraceptives
	Pregnancy
	Hormone replacement therapy
	Anti-phospholipid syndrome
	Myeloproliferative disorders
	Nephrotic syndrome
Inherited	
	Antithrombin deficiency
	Protein C deficiency
	Protein S deficiency
	APC resistance/Factor V Leiden
	Prothrombin 20210A allele
	Dysfibrinogenaemia
	Homocystinuria
	Thrombomodulin defect
Mixed	
	Hyperhomocysteinaemia
	High factor VII level
	High fibrinogen level

also well recognized. Other presenting features include thrombophlebitis, observed more commonly in association with protein C or protein S deficiency, the post-phlebitic syndrome, including venous ulceration over the internal malleolus. Warfarin-induced skin necrosis and neonatal purpura fulminans are rare manifestations of familial thrombophilia and there is recent evidence of an association with increased risk of fetal loss (Table 2). Although several studies have shown an association between arterial disease and familial thrombophilia, specifically factor V Leiden, the evidence is less clear than for venous thrombosis and the risk may be restricted to young individuals. Overall, approximately 55% of individuals with anti-thrombin, protein C and protein S deficiency give a history of venous thrombosis and in 80% of these the first thrombotic event occurs before the age of 40 years [1,2]. In individuals with factor V Leiden, the percentage of those having venous thrombosis is lower and the age of onset of the first thrombotic event later than with the other recognized causes of familial thrombophilia [1,2]. The thrombotic risk is greatly enhanced in subjects with combined defects and in those who are homozygous for factor V Leiden. In subjects with deficiencies of antithrombin, protein C or protein S, venous thrombotic events occur spontaneously in approximately 50%. In the remainder, other associated risk factors are evident. These include pregnancy, including the puerperium, surgery, oral contraceptive usage and prolonged periods of immobilization. It has been suggested that spontaneous venous thrombosis is less common in subjects with factor V Leiden [3]. Desmarais and colleagues [4] found that activated protein C resistance was a less important risk factor in unselected patients with pulmonary emboli (PE) and Manten using the factor V Leiden test found a weak association in a similar group of patients (relative risk of 3.3 for PE alone *versus* 6.9 for deep vein thrombosis (DVT) alone) [5]. These papers have shown that there may be subtle differences between risk factors leading to DVT and those leading to subsequent PE [4,5].

Anti-thrombin deficiency

Since its identification in 1965, numerous families with anti-thrombin deficiency have been reported [6,7] and a large number of causative mutations have been described [8].

Type I (quantitative defects) and IIRS (reactive site functional defect) are both associated with thrombophilia whilst type II heparin binding site defect (HBS) is not, at least in the heterozygous form. Antithrombin deficiency appears to be more clinically severe than deficiencies of protein C and protein S. The prevalence of anti-thrombin deficiency has been reported to be 4% amongst thrombophilic patients [9], 1% in patients presenting with a first DVT [10] and 0.02% in blood donors [11]. The 50-fold difference in the prevalence among patients with a first event DVT and that in the 'healthy' population of

Table 2 Clinical conditions associated with familial thrombophilia

Venous thrombosis
• lower limb
• pelvic
• mesenteric
• cerebral venous
• pulmonary embolus
Post-phlebitic syndrome
Leg ulcers
Warfarin-induced skin necrosis
Neonatal *purpura fulminans*
Recurrent fetal loss

blood donors, supports a higher thrombotic risk than other familial defects such as protein C deficiency. However, such a difference could not be found in a direct comparison in a population study,[9].

Protein C deficiency

Since its identification in 1981 numerous families with hereditary protein C deficiency have been reported [12–14]. Heterozygous deficiency increases the risk of thrombosis without any clear difference by type (type 1 – quantitative defect, type 2 – qualitative defect) of deficiency or by underlying mutation [15]. Family members with protein C deficiency have an 8–10-fold increased risk of venous thrombosis and by the age of 40, half of them will have experienced at least one thrombotic event [16,17]. This risk is similar to that observed in a population based study [10].

Protein S deficiency

The association between familial protein S deficiency and thrombosis was first described in 1984 [18]. At least 32 causative mutations in the protein S gene have been reported [1], a relatively small number in comparison to anti-thrombin and protein C mutations, owing to the complexity of the protein S gene. Three types of defect are recognized, type I (low plasma total and free protein S), type II (functional defect) and type III (low free protein S). Type I and type III deficiencies have recently been shown to be phenotypic variations of the same genotype [19] and many of the previously described type II defects are now known to represent activated protein C resistance and to have been previously misdiagnosed [20]. As the prevalence of protein S deficiency in the general population and the incidence rate in families is unknown, so the risk of thrombosis associated with protein S deficiency has not been quantified.

APC resistance

A single point mutation in the factor V gene (G1691A, factor V Leiden) [21] accounts for almost all the cases of true activated protein C resistance first described by Dahlbäck in 1993 [22]. This is the most frequent inherited defect associated with venous thrombosis and has been found in 20% of consecutive patients with a first DVT [23] (Table 3). It has been found in up to 7% of the healthy European population [24], but its prevalence varies greatly depending on the ethnic origin of the population studied [25].

Table 3 The currently accepted familial prothrombotic disorders, estimates of their frequencies in the general population, and among patients presenting with spontaneous venous thrombosis. (Composite data from [1,2,26] as well as unpublished observations)

Defect	Frequency in the general population	Frequency in patients with thrombosis
APC resistance/Factor V Leiden	3–6%*	20%
Prothrombin 20210A allele	1–2%	6%
Antithrombin deficiency	0.02%	1%
Protein C deficiency	0.2%	3%
Protein S deficiency	0.1%	1–2%
Dysfibrinogenaemia	<0.01%	<0.1%
Homocystinuria	<0.01%	<0.1%
Thrombomodulin mutations	<0.01%	<0.1%

*Caucasian populations

In a family study the risk of thrombosis was higher among affected relatives and approximately 25% of those affected had suffered a thrombosis by the age of 50 [24]. Although this risk is lower than that reported for familial protein C deficiency [17] the difference may be due to selection bias: because APC resistance is common, affected patients may not have been as highly selected as families with protein C deficiency in previous studies. In a population-based control study the relative risk for APC resistance was 7 whereas for protein C deficiency it was 6.5 suggesting that the two abnormalities do not differ in severity [10,26].

Prothrombin 20210 G>A

The most recent genetic factor to be associated with thrombosis was reported in November 1996 and is due to a single point mutation at position 20210 of the prothrombin gene [27]. This variant was detected in 6.2% of consecutive patients with thrombosis and in 2.3% of healthy control subjects, which yields a relative risk of 2.8 for carriers of the variant *versus* non-carriers [27]. This implies that it is a relatively frequent risk factor conferring a smaller risk than deficiencies of anti-thrombin, protein C, protein S or factor V Leiden. The 2.3% prevalence in the control population was based on 474 healthy subjects, but in a second subsequent sample

of 500 healthy individuals in Leiden, the incidence was less than 1% [28] which is similar to that found in Sheffield, UK (0.6% of blood donors). If the true prevalence is nearer 1%, this would yield a relative risk similar to those observed for the other thrombophilic factors referred to above. The prothrombin 20210A variant is closely linked to factor II levels, which, in turn, are associated with the increased risk of thrombosis (Table 4).

Other defects

A number of other rare inherited disorders are associated with venous thromboembolism (Table 1). These include dysfibrinogenaemia [29], homocystinuria due to cystathionine β-synthase deficiency [30] and thrombomodulin mutations [31,32].

Other genetic defects such as deficiencies of plasminogen, heparin cofactor II and factor XII [1] have been suggested to be associated with venous thromboembolism but evidence for a causal relationship is lacking.

Increased levels of FVIII [33] and homocysteine [34,35] have been shown to be associated with venous thrombosis but these levels are strongly influenced by environmental factors and the contribution of genetic factors is uncertain. Factor VIII levels exceeding 150 IU/dL, found in 11% of the population, are associated with a six-fold increase in the risk of thrombosis [33]. Hyperhomocysteinaemia (defined as a level above the 95th percentile: i.e. exceeding 18.5 μmol/L) was found to be associated with a 2.5-fold increased risk of deep vein thrombosis [34].

Table 4 Prothrombin levels, prothrombin genotype and risk of thrombosis

Plasma prothrombin level IU/dL	Relative risk (OR)	Prevalence of 20210A genotype	
		Patients (%)	Controls (%)
<95	1	0	0
95–104	1.3	2.8	0
104–115	1.4	6.9	1.7
>115	2.2	18.2	9.3

Results for 424 patients and 474 controls for whom DNA was available and none of whom were on oral anticoagulant therapy [27].

Combined defects

Although combined defects of anti-thrombin, protein C and protein S deficiency have been reported, they are extremely rare due to the low allelic frequency of each of these defects. Factor V Leiden, however, is fairly common and patients with combinations of this and anti-thrombin, protein C and S deficiency have been reported. Homozygous patients with protein C or S deficiency have a severe phenotype with thrombosis developing shortly after birth (*purpura fulminans*). Patients homozygous for factor V Leiden are more common and have a thrombotic risk ten times higher than heterozygous patients [28]. The reports on patients with combined defects all suggest that the thrombotic risk is higher than persons with a single defect [28]. In thrombophilic families with protein C deficiency and Factor V Leiden, for example, a history of thrombosis was present in 31% of individuals with only protein C deficiency, in 13% of those with only factor V Leiden and in 73% of those with both defects [36,37,28]. A similar increase in risk was reported in patients with factor V Leiden combined with antithrombin deficiency [38] or with protein S deficiency [39].

Risk assessment, oral contraceptives and pregnancy

In The Netherlands, the estimated incidence of venous thrombosis among women not taking oral contraceptives is 0.8 per 10 000 women years [40]. This compares with a lower estimate of 0.4 per 10 000 in a slightly younger group of women reported from the UK [41]. In the Dutch study the incidence of DVT rose to 3.0 per 10 000 women years among users of oral contraceptives with a further increase to 28.5 per 10 000 women years among oral contraceptive users who also possessed the factor V (Leiden) mutation. The incidence of DVT among women with the factor V mutation but who were not taking oral contraceptives was 5.7 per 10 000 women years. On the assumption that the case fatality of venous thrombosis among young adults is 2% this would mean that for carriers of the factor V mutation, the usage of combined oral contraceptives for 12 months would result in a death rate, from pulmonary embolism of 5.7 per 100 000. When providing counselling in respect of the venous thrombotic risk among oral contraceptive users it is important to appreciate ethnic/geographical differences in the prevalence

of the factor V mutation. Thus, prevalences of 3%, 6% and 15% have been reported in The Netherlands, USA and Southern Sweden, respectively. In contrast, the prevalence of the factor V mutation in Asia and Africa appears to be extremely low. Current data do not point to an immediate need for widespread screening of women asking for the oral contraceptive pill.

When providing counselling it is important to appreciate that, at least in men, a previous venous thrombosis is a strong risk factor for a further thrombotic event. Although it remains to be established, it would be surprising if this did not also pertain to women.

Venous thromboembolism, including fatal pulmonary embolism, is an important cause of morbidity and mortality in pregnancy. The pregnancy-associated thrombotic risk persists for at least 6 weeks after delivery. Although detailed information is limited, the available evidence suggests that the pregnancy-associated thrombotic risk is greater in women with anti-thrombin deficiency than in those with deficiencies of either protein C or protein S [42]. In Sweden, a diagnosis of APC-R was made in 60% of women who developed a first episode of venous thrombosis during pregnancy. Decisions regarding the use and timing of thromboprophylaxis for pregnant women with familial thrombophilia are likely to be influenced by the nature of the defect and whether this is present alone or in combination with other genetic and acquired prothrombotic risk factors. Consideration should be given to the previous thrombotic history, particularly in relation to oral contraceptive usage and previous pregnancies. The obstetric history of other affected family members may also influence decision-making.

A number of different thromboprophylactic regimes have been used during pregnancy. Until recently many favoured the use of heparin in the first and third trimesters with warfarin being substituted in the second trimester. At present, more clinicians are recommending heparin for the entire pregnancy with conversion to warfarin for a period of approximately 2 months after delivery. Both unfractionated and low molecular heparins are used, the latter having the advantage that monitoring is considered unnecessary. Women with anti-thrombin deficiency appear to be at a particularly high risk of thrombosis during pregnancy and the puerperium and it is worth considering the use of anti-thrombin concentrate at delivery.

Recent evidence for an increased risk of fetal loss in women with familial thrombophilia may also influence decision-making in respect of anti-coagulant therapy during pregnancy [43].

Women receiving oral anti-coagulants and contemplating pregnancy pose a particularly difficult problem as the beneficial anti-thrombotic action of coumarins needs to be weighed against their potential embryopathic effects. One possible strategy is to discontinue the warfarin and substitute heparin. Although this is undoubtedly beneficial for the foetus, the prolonged exposure to heparin may be complicated by unacceptable osteoporosis.

Prevention of thrombosis

In the short term, prevention involves avoidance of risk factors, the use of graduated elastic stockings and subcutaneous unfractionated or low molecular weight heparin at times of increased risk. Ultimately the long-term prevention of thrombosis, apart from avoidance of high-risk situations, centres around the use of oral anti-coagulants. The benefit of these agents has to be balanced against inconvenience, cost and the risk of bleeding whilst on warfarin. In non-thrombophilic patients life-long oral anticoagulation is offered to those with two or more spontaneous thrombotic events or those with a single life-threatening thrombotic event. An important question is whether patients with thrombophilia should be managed differently. It is not possible to make definite recommendations at present due to the lack of published data.

Management of acute thrombosis

The management of acute thrombosis in a patient with familial thrombophilia, is usually identical to that of patients without inherited defects. Unfractionated heparin is infused at 1300 U per hour following an initial bolus of 5000 U aiming to maintain the APTT ratio at 1.5–2.5. Warfarin is commenced on the first day of heparin treatment. In view of the risk of warfarin-induced skin necrosis (see later) a smaller loading dose, than the usual 10 mg daily, is given in protein C and S deficient patients. Heparin is given for at least 5 days or until the INR is >2.0. The therapeutic range for first thrombotic events is around 2.0–3.0.

Rarely, patients with anti-thrombin deficiency require very high doses of heparin to achieve ade-

quate anti-coagulation, a phenomenon known as heparin resistance. Although an anti-thrombin concentrate is available, its value has not been assessed in randomized trials. It is reasonable to use the concentrate where adequate anti-coagulation can not be achieved with heparin alone or where there is clinical extension or recurrence despite adequate anti-coagulation.

Patients with familial thrombophilia and a first thrombosis should be anti-coagulated for 6 months using a therapeutic ratio of around 2.0–3.0. In non-thrombophilic patients, 6 months anti-coagulation has been shown to be superior to 6 weeks [44]. This, together with the fact that thrombophilia is a permanent risk factor suggests that at present 6 months should be the optimal anti-coagulation of these patients. For patients with more than one thrombosis, life-long anti-coagulation should be offered. Recently Shulman and colleagues have shown that long-term anti-coagulation is more effective in reducing the risk of recurrence after two events than short-term treatment [45].

Purpura fulminans

Neonatal *purpura fulminans* is characterized by the development of skin and systemic thrombosis in neonates due to homozygous or compound heterozygous protein C or protein S deficiency. Although fresh frozen plasma has been used successfully to treat this condition, the current treatment of choice is protein C concentrate which is virally inactivated and has the additional advantage of being available at a high concentration [46].

Warfarin-induced skin necrosis

A rare complication of warfarin therapy is skin necrosis that occurs soon after initiation of therapy with this agent. It has been described in protein C deficiency, which accounts for a third of all reported cases [47], in protein S deficiency [48] and in activated protein C resistance [49]. Warfarin-induced skin necrosis (WISN) classically occurs in the first week after warfarin initiation, more commonly affects females and involves the fatty parts of the body such as the thighs and breast. WISN is believed to be due to the more rapid fall in plasma concentrations of the vitamin K-dependent, naturally occurring anti-coagulants (protein C and S) compared to the fall in the levels of factors II, VII, IX and X. This temporary dissociation results in a hypercoagulable state which leads to thrombosis of the dermis and subcutaneous fat. It can be prevented by the use of smaller loading doses of warfarin which initially produce slower anti-coagulation, and by the use of concomitant heparin therapy at the time of warfarin initiation. Protein C concentrate is available and has been used in established WISN associated with protein C deficiency [50].

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