Unsolved issues in etiology and treatment of venous thrombosis

Wichers, I.M.

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Introduction

I.M. Wichers, S. Middeldorp
The elucidation of the genetic basis of venous thromboembolism started in 1965 with the discovery of antithrombin deficiency by Egeberg and has advanced considerably in recent years. While known genetic defects (deficiencies of antithrombin, protein C and protein S, mutations (Factor V Leiden, prothrombin G20210A mutation) are present in 30-40% of the patients with venous thromboembolism, it has been shown that other genes are likely to be involved in another 25-30% of the patients. Thus, our knowledge about the genetic basis of venous thromboembolism remains incomplete.

Outline of this thesis
Chapters 2 to 6 describe the Genes study, which was set up in 2002. The aim of this study was to identify new hereditary risk factors for venous thromboembolism by analyzing families with an increased propensity for developing venous thrombosis, without any of the known hereditary risk factors.

The second part of this thesis (Chapters 7 to 10) focuses on superficial vein thrombosis. Superficial vein thrombosis has traditionally been regarded as having another etiology than venous thromboembolism, but comparable risk factors are involved in both diseases. The idea that superficial vein thrombosis is a benign disease appears to be inappropriate. Firstly, superficial thrombi carry a risk of progressing to the deep venous circulation. Secondly, superficial vein thrombosis often recurs or progresses causing a burden for the patient in terms of pain symptoms and the need for escalation of therapy.

Part I: Genes in venous thromboembolism

From single-gene to multi-genetic to just complex
Genetic research has been successful in so-called Mendelian genetic disorders, which have almost all been mapped now. Although devastating in disease development, these disorders are often very rare. Common diseases mostly have a much more complex etiology, due to a mix of environmental and genetic factors.

Traditionally, inherited venous thromboembolism has been attributed to single genetic defects. This remains partly true for the homozygous thrombophilic defects in which homozygosity is incompatible with life (antithrombin deficiency) or causes massive
venous thrombosis or purpura fulminans in newborns (protein C and S deficiency). Homozygosity for factor V Leiden or the prothrombin G21020A mutation has a milder phenotype, although risk of venous thromboembolism is strongly increased as compared to non-carriers (e.g. 50-100 times in homozygous FVL). The discrepancy between population-wide risk of venous thromboembolism (i.e. 0.1%) and gene frequency of factor V Leiden (5%) has led to the understanding that venous thromboembolism must be a multigenetic disease.

Genetic susceptibility
Estimating the proportion of genetic variance over the total phenotypic variance can be done by studying monozygotic or dizygotic twins, or by statistical methods calculating heritability. A study in Danish twins showed that for venous thromboembolism the proportion of the variance attributable to genetic effects was as high as 55%. Furthermore, in the Genetic Association of Inherited Thrombophilia (GAIT) study, the heritability of thrombosis susceptibility was estimated by means of a novel variance component method using a multivariate threshold model. It was estimated that more than 60% of the variation in susceptibility to common thrombosis is attributable to genetic risk factors. A large French-Canadian protein C deficient family was shown to have a second unknown defect, which interacted with the protein C mutation increasing the risk of venous thromboembolism. This explained the increased risk of venous thromboembolism found in family members in the same kindred without the protein C mutation compared with the normal population. However, heritability estimates remain approximations of the genetic variance in disease risk, that are unable to effectively separate shared genetic from shared environmental or nongenetic influences.

The GENES study
The main objective of the GENES study was to identify novel hereditary thrombophilic defects by defining an intermediate (or subclinical) phenotype. An intermediate phenotype would help to distinguish individuals with a persistent (genetically determined) hypercoagulable state from those without. We used a similar approach as has been carried out successfully in families with familial dyslipidemias. Probands
and their family members were identified by specially trained genetic field workers. This has resulted in efficient screening of familial hypercholesterolaemia and led to the discovery of new genes in patients with low levels of HDL cholesterol such as the ABCA1 gene.

Inclusion criteria for the GENES were a history of venous thromboembolism and the absence of known thrombophilic defects (factor V Leiden, deficiencies of protein C, of protein S and of antithrombin, the prothrombin G20210A mutation and (familial) elevated levels of factor VIII, IX and XI). A standardized history was obtained using a validated questionnaire. Family members were defined as cases if they had had a history of symptomatic venous thromboembolism.

Two different approaches were undertaken to define an intermediate phenotype in the families. Firstly, by assessing several coagulation and fibrinolysis assays in all members of the families (chapter 2). We hypothesized that these tests could give an overall impression of a hypercoagulable or hypofibrinolytic state. In addition, a protein profile analysis was performed using surface-enhanced laser desorption/ionization-time of flight mass spectometry (chapter 3). Proteins involved in coagulation have been widely investigated and none have thusfar been found useful as (part of) a subclinical phenotype. Therefore, we were interested in finding proteins from other biosystems, such as inflammation, involved in venous thrombosis by performing protein profile analysis. Furthermore, we assessed the heritability of the coagulation and fibrinolysis assays, and protein profiles.

The second approach was the performance of a whole genome scan in all thrombophilic families (chapter 4). If a gene is contributing to the development of disease, the region of the genome in which the gene is lying will be co-inherited more frequently than is expected by chance. A genome scan recognizes commonly inherited regions by following the inheritance of polymorphic microsatellite markers in affected members of a pedigree. Several whole genome scans have been performed in thrombophilic families. In these independent studies a region on chromosome 18 was found to be linked to the risk of developing venous thromboembolism. Chapter 5 evaluates whether linkage of venous thrombosis to chromosome 18 could be confirmed in the GENES study. In chapter 6 a whole genome scan (quantative trait linkage analysis) performed in the GENES study is described.
Part II: Superficial vein thrombosis

Terminology
Synonyms for superficial vein thrombosis of the leg are superficial phlebitis and superficial thrombophlebitis. In general “superficial phlebitis” refers to the clinical findings of inflammation such as pain, tenderness or erythema along the affected superficial vein, often palpable as a cord. The term “superficial thrombophlebitis” or superficial vein thrombosis is used when a thrombus is found by diagnostic testing such as compression ultrasonography or phlebography.

Background
The fact that there are several synonyms for superficial vein thrombosis illustrates the lack of precise knowledge about this disease. The incidence of superficial vein thrombosis for example, is not well-known, although is estimated to be higher than that of deep vein thrombosis. The diagnosis is often made in a general practice setting, where no incidence studies are available. If referred, patients are generally sent to specialists from various disciplines, such as surgery, dermatology, internal medicine etc. Traditionally, superficial vein thrombosis has been regarded as benign, i.e. selflimiting without risk of extension into the deep venous system. However, there are no epidemiological studies to confirm this view and several clinicians have a different experience. 12;13;15;30

Risk factors for superficial vein thrombosis and risk of venous thromboembolism
Superficial vein thrombosis and venous thromboembolism have traditionally been regarded as different in etiology. However, they share the same risk factors, i.e. postoperative states, pregnancy, active malignancies, auto-immune diseases, use of oral contraceptives, previous venous thromboembolism and varicosity. 14 Also, inherited thrombophilic defects such as the factor V Leiden and prothrombin 20210A mutations as well as deficiencies of the natural anticoagulant proteins C and S and antithrombin are found more often in patients with superficial vein thrombosis than in healthy individuals. 6;7
Location of superficial vein thrombosis is thought to influence the risk of progression to a deep venous thrombosis and/or embolization to the pulmonary arteries. Superficial vein thrombosis of the vena saphena magna or close to the saphenous-femoral junction has the highest risk of developing venous thromboembolism. Furthermore, superficial vein thrombosis can recur and cause discomfort and in some cases might be a first symptom of cancer. We evaluated the risk of developing venous thromboembolism following superficial vein thrombosis (chapter 7).

**Treatment of superficial vein thrombosis**

A wide range of therapies have been described for superficial vein thrombosis. In general, superficial vein thrombosis is either not treated or treated with elastic compression stockings, topically (e.g. diiodor creams) or with non-steroidal anti-inflammatory agents. Although pain is regarded to be the most important symptom, the knowledge that superficial vein thrombosis may increase the risk of venous thromboembolism, more aggressive approaches treatments became more common. Active treatments range from surgical ligation or stripping of the affected veins to full-dose anticoagulant therapy. In order to summarize the evidence about the treatment of superficial vein thrombosis with the aim to prevent extension or recurrence, we performed two reviews. The first review concerns treatment (non-surgical or topical) options for superficial vein thrombosis (chapter 7), the second review, a Cochrane review, investigated all treatment options, i.e. medical (topical, oral, subcutaneous) and surgical for superficial vein thrombosis (chapter 8). A retrospective cohort study was performed to determine the risk of arterial and venous complications after a superficial vein thrombosis in Chapter 9. Furthermore, a retrospective follow-up study was performed to evaluate therapeutic management, thrombophilic risk factors and clinical outcome of superficial vein thrombosis in one clinic over the past six years (chapter 10).
Chapter 1

References


