Unsolved issues in etiology and treatment of venous thrombosis

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Publication date
2010

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Summary

This thesis aimes to address two issues of venous thrombosis. The first concerns the etiology of venous thromboembolism (VTE). A search was performed for new hereditary risk factors of this disease by studying families with unexplained thrombophilia: the GENES study. The second issue involves the treatment of superficial vein thrombosis (SVT). Treatment options for SVT were systematically reviewed and etiology and treatment of disease were retrospectively studied in a general practice and hospital setting separately.

Part I : GENES study

Although several inherited risk factors associated with VTE have been discovered, it has been argumented that more genes are involved in the pathogenesis of this disease. The GENES study was set up to identify new hereditary risk factors for VTE in families with unexplained thrombophilia. However, the lack of an intermediate phenotype in VTE impedes the discovery of new familial risk factors. Therefore we set out to define an intermediate phenotype for VTE by performing global coagulation analyses in the GENES study in **Chapter 2**. Coagulation assays were performed in 353 individuals (17 families) of whom 41 (12%) had a history of VTE. We found that an increased ETP (OR 1.03 for each % increase, 95% CI 1.01-1.05) may serve as an intermediate phenotype for VTE. Also, a high variance attributed to genes for the ETP was found in one particular family (68%). Because we were interested to know if one or more coagulation variables determined the ETP in this family, these were studied in **Chapter 3**. In multiple linear regression analysis prothrombin time (PT), factor VII, factor VIII, factor IX and antithrombin were found to be minor determinants of the ETP. However, none of these variables were independent determinant of the ETP. Therefore, the ETP seems to be an independent risk factor for thrombosis.

In **Chapter 4**, we report the search for proteins of biosystems outside the coagulation cascade that have discriminative value for venous thrombosis, using new proteomic techniques. Sera of 491 individuals selected from 29 families with unexplained thrombophilia were analysed by surface enhanced laser desorption/ionisation-time of flight (SELDI-TOF) mass spectometry. Of the 69 peak clusters detected, three differed

significantly in expression between individuals with a history of VTE and those without. One of the peaks was found to be significantly discriminative in the multivariate analysis, but unfortunately specificity and sensitivity remained insufficient.

A candidate region for genes involved in the risk of venous thrombosis on chromosome 18 was identified in a whole genome scan performed in a large protein C deficient kindred. These data were confirmed in another thrombophilic family study (GAIT study). We performed linkage analysis of venous thrombosis in the same region (chromosome 18) in the GENES study to find support for these findings in **Chapter 5**. Two-point linkage analysis was performed using venous thrombosis and several coagulation and fibrinolysis factors as a trait. No linkage was found for any of the traits (clot lysis time (CLT), ETP, thrombin generation time (TGT), activated protein C-sensitivity ratio (APC-sr), prothrombin fragment 1+2 (F1+2) and venous thrombosis) at D18S53 or D18S843 in the whole study population. In **Chapter 6** a genome-wide (variance components) linkage analysis for symptomatic VTE and for several coagulation variables was performed in 22 families (304 individuals), including the family (128 individuals) that had a high heritability estimate for the ETP. Suggestive linkage peaks (LOD-score 2.0, 1.9 and 2.5) were found on 11q23, 20q13 and 1q23 for VTE, ETP and APC-sr, respectively. Linkage analysis in the family of 128 individuals revealed significant (LOD > 3.3) linkage peaks on 16q22, 16q23, 17q22 and 20q11 for factor II, factor V, PT and protein C respectively. A suggestive linkage peak (LOD-score 2.6) was found on 20q11for ETP. For VTE, we confirmed a linkage peak locus at 11q23 that was previously reported.

Future perspective

Although the families in the GENES study proved to be a valuable resource for the analyses as previously described, this has not led to the identification of new heritable defects. However, several interesting results warrant further research, e.g. the finding that a high protein C levels in one particular family is strongly influenced by genes and several quantative trait loci in the genetic linkage analysis.

Part II: Superficial vein thrombosis

Venous thromboemblism has been investigated extensively, but very little is known about superficial vein thrombosis (SVT). Traditionally, SVT has been regarded as strictly benign, but there is an underestimated risk of recurrence and progression, in several cases leading to VTE. **Chapter 7** is a systematic review on the treatment of SVT. The aim of the review was to collect evidence from randomized clinical trials concerning the efficacy and safety of medical or surgical treatments of SVT for the prevention of DVT and PE. Five studies were included. Pooling of the data was not possible due to the heterogeneity among the studies. Moreover, three studies had major methodological drawbacks limiting the clinical applicability of the results. One of the remaining (pilot) studies showed a non-significant trend in favor of high- compared to low-dose unfractionated heparin for the prevention of VTE. The last remaining study showed a non-significant trend in favor of a short term treatment with low-molecular-weight heparin (LMWH) or a non-steroidal anti-inflammatory drug (NSAID) as compared to placebo shortly after treatment with respect to VTE, but the apparent benefit disappeared after three months of follow-up. Active treatment of SVT reduced the incidences of extension or recurrence. Given the current lack of solid evidence we suggest that patients with SVT should be treated with – at least – intermediate doses of LMWH.

In **Chapter 8** a Cochrane review to assess the efficacy and safety of topical, medical, and surgical treatments in patients presenting with SVT of the legs is described. Twenty-five studies involving 2509 patients with SVT of the legs were included in this review. Pooling of the data and subgroup analysis were not possible given the heterogeneity of the included studies. Moreover, the methodological quality of most of the trials was poor. Treatment ranged from LMWH, to anti-inflammatory agents, topical treatment, surgery and a plethora of other oral, intramuscular, and intravenous treatments. Both LMWH and NSAIDs significantly reduced the incidence of SVT extension or recurrences by about 70% as compared to placebo. No major bleeding was reported in any of the studies evaluating LMWH and NSAIDs. Furthermore, LMWH and NSAIDs seemed to have a similar efficacy and safety. However, the studies that evaluated these treatments had a relatively small sample size, which did not allow an adequate

comparison between LMWH and NSAIDs. Overall, topical treatments improved local symptoms. However, no data were provided on the effects of these treatments on VTE and SVT extension. Surgical treatment combined with elastic stockings in SVT was associated with a lower VTE rate and progression of SVT, as compared to elastic stockings alone. In addition, a relatively small study suggested that surgery may have a comparable efficacy and safety profile to LMWH. Currently, LMWH and NSAIDs appear to be best therapeutic options for SVT of the legs. While the available data are too limited to make clear recommendations, an intermediate dose of LMWH for at least a month might be advised.

A historic follow-up study to determine the risk of arterial and venous complications after a SVT in the leg in the general practice population is reported in **Chapter 9**. Patients with SVT were identified through a meticulous search of the medical registers of 40,013 patients, enlisted with five health-centers in Amsterdam, the Netherlands. Outcomes were DVT, PE, acute coronary events or ischemic stroke over a 6 months follow-up period. Odds ratios were used to quantify the associations between SVT and these outcome events. Exposed patients had a ten-fold (95% confidence interval 2.0 – 51.6) increased risk of developing DVT during the follow-up time compared to the non-exposed individuals. No enhanced risk for PE, acute coronary events or ischemic stroke could be detected. SVT is a clear risk factor for DVT. Although effective treatments for the prevention of DVT are available the absolute risk is too low to advocate prophylaxis in a general practice population.

In **Chapter 10** we retrospectively evaluated therapeutic management, thrombophilic risk factors and clinical outcome of SVT. In 73 patients follow-up information was present (3/76 non-evaluable patients). In 9/32 (28%) patients treated with carbasalate calcium there was progression of SVT as assessed by ultrasonographic evaluation, compared to 3/11 (27%) in the LMWH group and 3/6 (50%) in the no treatment group. DVT was diagnosed in 5/36 (14%) patients treated with carbasalate calcium compared to 1/13 (1%) in the LMWH and other treatment group (e.g. hiroid cream) at follow-up. Furthermore, one or more thrombophilic defects were present in twenty of thirty-six patients tested. The results of our study show that patients with superficial vein thrombosis may be at risk for progression to venous thromboembolism and therefore need to be treated or carefully followed.

Future perspective

Considering the amount of scientific attention given to VTE in the passed decade, it is surprising that research into the superficial counterpart of this disease has only recently begun. One of the possible reasons for this could be that SVT is mostly seen in general practice where less diagnostic investigations and research take place compared to specialist care. As a result, an evidence-based guideline on diagnosis and treatment of superficial vein thrombosis is lacking. Results from a large double-blind randomized trial are underway, in which a prophylactic dose of fondaparinux is compared with placebo (CALISTO trial). Hopefully, this will lead to an evidence-based and rational approach to patients with SVT.