Review Article

Do prothrombotic factors influence clinical phenotype of severe haemophilia? A review of the literature

Karin van Dijk[1,2], Johanna G. van der Bom[1,3], Kathelijn Fischer[1,4], Diederick E. Grobbee[2], H. Marijke van den Berg[1,4]

[1]Van Creveldkliniek, Dutch National Hemophilia Treatment Center, UMC Utrecht, The Netherlands
[2]Julius Center for Health Sciences and Primary Care, UMC Utrecht, The Netherlands
[3]Department of Clinical Epidemiology, Leiden UMC, The Netherlands
[4]Wilhelmina Children's Hospital, UMC Utrecht, The Netherlands

Summary

There is considerable variability in bleeding patterns of severe haemophilia (<1% factor VIII). Knowledge of the contribution of thrombophilic factors in these patterns may improve individually tailored treatment strategies. We reviewed the literature regarding the relation between prothrombotic factors and clinical phenotype of severe haemophilia. Medline and EMBASE were searched for relevant articles. 9369 articles published between 1963 and September 2003 were screened and seven relevant papers were retrieved. Each of these reported on a different combination of thrombophilic factors. Presence of the factor V Leiden mutation appears to decrease the severity of severe haemophilia most consistently. Findings on other thrombophilic factors were inconclusive. There is a clear need for additional research on potential determinants of phenotypes of severe haemophilia before such knowledge can be translated into individual care for severe haemophilia patients with confidence.

Keywords

Severe haemophilia, phenotype, prothrombotic factors

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Introduction

There is considerable variability in bleeding pattern, and age of first bleeding in patients with severe haemophilia (<1% factor VIII). Forty-four percent of severe haemophilia patients experience their first bleeding episode within the first year of life, whereas others do not bleed before the age of four (1). Ramgren et al showed that the age of the first symptom was 3 to 5 years in 3 out of 71 patients and 6 to 7 years in 1 out of 71 patients (2). Rainsford et al distinguished between patients with a severe and those with a less severe bleeding pattern, and described that 45% of the patients with severe haemophilia had a 50% lower joint bleed frequency than the other 55% (3). In a cohort of severe haemophilia patients without intensive treatment, Aledort et al showed that approximately 10% had 6 normal joints (4). Additionally, 9% of young adults with severe haemophilia from France treated on demand did not have any joint bleeds (5).

To improve cost-effectiveness in the care of severe haemophilia patients, individualised treatment is of critical importance (6, 7). Knowledge of the determinants of bleeding patterns of severe haemophilia patients may help to optimise individual treatment strategies for these patients. Recent studies have suggested that prothrombotic factors may modify the clinical phenotype in severe haemophilia A (8, 9).

We reviewed published evidence regarding the relation between the clinical phenotype of severe haemophilia and prothrombotic factors.

Correspondence to:
K. van Dijk, MD
Van Creveldkliniek, UMCU
Room C01.425
PO-Box 85500
3508 GA Utrecht
Tel.: +31-30-2508441, Fax: +31-30-2505438
E-mail: K.vanDijk@azu.nl

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Methods

Medline was searched from 1963 to September 2003 for original articles of observational studies regarding thrombophilia and variation in clinical phenotype among severe haemophilia patients. The following terms were used for the Medline search: severe haemophilia A, severe haemophilia, severe hemophilia, severe hemophilia A, haemophilia A, hemophilia A. Due to inconsistency in the Medline index regarding thrombophilia, clinical profile, bleeding frequency, joint status, and clotting factor consumption, a more specific search strategy was not available. All articles in English, Dutch, German, French, Italian and Spanish were screened. Letters, editorials and comments were excluded, as well as *in vitro* studies and animal studies. The reference lists of the identified articles were scanned for additional potentially relevant publications. EMBASE was searched from 1974 to 2003 for additional studies.

Inclusion criteria were original articles of observational studies regarding thrombophilia and variation in clinical phenotype among severe haemophilia patients (<1% factor VIII). Therefore, we excluded articles dealing with differences between mild, moderate and severe haemophilia.

Our search revealed a total of 9331 articles in Medline, and 107 articles in EMBASE. Ninety-six were duplicates, leaving 9369 articles for evaluation. Only eleven articles met the inclusion criteria (8-18).

Three were excluded because they addressed variation between mild, moderate and severe haemophilia patients instead of variation among severe haemophilia patients (9, 16, 18), leaving 8 studies for analysis. Two articles published overlapping study populations (12, 14). The largest and most recent study was considered in this review (14).

Results

An overview of the determinants studied in the seven reports is given in Table 1.

Inherited thrombophilic disorders

Activated protein C resistance and factor V Leiden (FVL)

Resistance to the anticoagulant effect of activated protein C is most commonly due to the FVL mutation (= Arg506Gln mutation). The FVL mutation is associated with thrombophilia (19, 20).

Arbini et al (10) selected severe haemophilia patients with a milder phenotype according to clinical parameters and, in contrast to expectations, found a low prevalence of FVL among these patients. Lee et al (8) compared severe haemophilia A phenotypes of 6 carriers of the FVL mutation and 131 non-carriers. Patients with the FVL mutation had lower factor concentrate utilization and fewer bleeding episodes. In a cohort study by Nowak-Gottl et al (14) the first symptomatic bleeding leading to the diagnosis of severe haemophilia occurred later in life in children with FVL mutation, the prothrombin G20210A mutation, protein C deficiency, the MTHFR mutation or an elevated lipoprotein a than in non-carriers of these factors. Ghosh et al (13) described 11 patients with a milder clinical presentation of severe haemophilia. Eight of these patients had one or more prothrombotic factors. One of them had the FVL mutation. No data were given on the prevalence of the FVL mutation among the 250 severe haemophilia patients with the more severe clinical presentation of severe haemophilia A. Grünewald et al (15) compared clotting characteristics and prothrombotic factors of severe haemophilia patients with a milder bleeding pattern and more severe bleeding pattern. Patients

	(n)	Arbini (21)	Lee (137)	Ghosh (11)	Grünewald (21)	Nowak-Göttl (103)	Ahmed (48)	Petkova (31)
Genetic factors	FVL	+	+	+	+	+	+	+
	PT G20210A mutation	-	-	-	+	+	+	-
	MTHFR C677T mutation	-	-	+	+	+	+	-
Plasma factors	low antithrombin	+	-	+	+	+	-	-
	low protein C	+	-	+	+	+	-	-
	low protein S	+	-	+	+	+	-	-
	hyperfibrinolysis	-	-	-	+	-	-	-

FVL = Factor V Leiden = Factor V G1691A mutation
PT G20210A = prothrombin G20210A
MTHFR C677T mutation = methylenetetrahydrofolate reductase
+ = studied
- = not studied

Table 1: Overview of prothrombotic factors studied as modifiers of haemophilic phenotype.

carrying either the FVL mutation or the prothrombin G20210A mutation or the homozygous MTHFR mutation were more often milder bleeders than patients without these mutations. None of the 27 severe haemophilia patients with a severe phenotype of severe haemophilia and none of the 14 patients with a milder phenotype were carriers of the FVL mutation in a study conducted by Ahmed et al (17). In a study by Petkova et al (11) 3 out of 31 severe haemophilia patients had a milder clinical phenotype. None of these patients and one of the patients with a more severe clinical phenotype were carriers of the FVL mutation.

Prothrombin G20210A mutation

Prothrombin is the circulating precursor of thrombin, which plays a role in fibrin formation. The A allele of a genetic variant (20210 G/A) in the 3'-untranslated region of the prothrombin mRNA has been associated with elevated plasma prothrombin levels and with an increased risk for venous thrombosis (21).

This mutation was studied by Nowak Göttl et al (14), Grünewald et al, and Ahmed et al (15, 17). The mutation was analysed separately from the other prothrombotic risk factors by Grünewald et al. They did not find a difference in the distribution of the prothrombin G20210A (PT G20210A) mutation among severe haemophilia patients with or without a milder clinical phenotype. Ahmed et al found this mutation in neither 27 severe haemophilia patients with a milder phenotype nor in 14 with a more severe phenotype.

Protein C deficiency, protein S deficiency and antithrombin deficiency

Protein C, protein S and antithrombin down-regulate activated factor V and activated factor VIII. It is well established that congenital deficiencies of protein C, protein S and antithrombin are associated with an increased risk of venous thrombosis. Whether they are associated with variation in phenotype of severe haemophilia is less clear.

Protein C: Twenty-eight children with severe haemophilia A carrying either the FVL mutation, the prothrombin G20210A mutation, a deficiency of protein C, the MTHFR mutation or who had an elevated lipoprotein a, had their first bleed significantly later in life than 75 children without these factors (14). One patient with protein C deficiency and antithrombin deficiency appeared to have a relatively mild clinical phenotype (13). Grünewald et al did not find a statistically significant difference in protein C antigen or activity between patients with mild and severe bleeding pattern. Arbini et al did not find any patients with protein C deficiency among the patients in their study.

Protein S: Grünewald et al did not find a statistically significant difference in protein S antigen or activity between patients with mild and severe bleeding pattern. In the study by Ghosh et al two patients with a milder clinical pattern had protein S deficiency in combination with heterozygous MTHFR mutation. Protein S deficiency was not found in patients with a more severe clinical pattern. None of the patients studied by Arbini et al and Nowak-Gottl et al was diagnosed with protein S deficiency.

Antithrombin: Antithrombin deficiency, combined with protein C deficiency was found by Ghosh et al in one patient with a milder clinical phenotype and not in patients with a more severe phenotype. Grünewald et al did not find a significant difference in antithrombin activity between patients with mild and severe bleeding pattern. None of the patients studied by Arbini et al and Nowak-Göttl et al had antithrombin deficiency.

Methylenetetrahydrofolate reductase (MTHFR) C677T variant

Mild hyperhomocysteinemia is associated with both artherothrombosis and venous thrombosis (22). Methylenetetrahydrofolate reductase (MTHFR) catalyses the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the cofactor for the methylation of homocysteine to methionine. Individuals with the thermolabile variant of MTHFR have decreased MTHFR activities, resulting in elevated plasma homocysteine concentrations (23). A homozygous 677C → T transition in the MTHFR gene has recently been identified as the cause of reduced enzyme activity and thermolability of the protein (24). Homozygosity for the MTHFR mutation is associated with elevated plasma homocysteine concentrations (24, 25). However, this homozygous mutation is not associated with an increased risk of deep-vein thrombosis, whereas mild hyperhomocysteinemia is (26, 27).

Ghosh et al only found patients who were heterozygous for this mutation. Heterozygosity for this mutation is not associated with increased risk for thrombosis. Grünewald et al reported three patients with a homozygous mutation. Patients carrying the FVL mutation, the prothrombin G20210A mutation or the homozygous MTHFR mutation were more often milder bleeders than patients without these mutations. Nowak-Gottl et al found 10 patients who were homozygous for this mutation. The first symptomatic bleeding leading to the diagnosis of severe haemophilia in children with a prothrombotic factor (FVL-, prothrombin G20210A-, or the MTHFR mutation or protein C deficiency) occurred later in life than in children without these factors. Ahmed et al described the relation between the homozygous MTHFR mutation and clinical phenotype of severe haemophilia. In their study of 48 severe haemophilia patients, two out of 14 "milder" haemophilia patients and none out of 27 "more severe" patients carried the homozygous MTHFR mutation, suggesting a protective effect of this mutation.

Coagulation factors

Thrombin generation

Elevated endogenous thrombin potential has been associated with thrombosis and cardiovascular disease (28). The major

defect in haemophilia is the decreased ability to generate sufficient thrombin (29). Median prothrombin fragment 1+2 concentration, a direct marker of thrombin generation, was 0.66 (interquartile range (IQR) 0.51-0.77) in 8 patients with a more severe phenotype, 0.52 (IQR 0.41-0.53) in 10 patients with a milder phenotype and 0.83 (IQR 0.59-0.95) in the reference population (15). Endogenous thrombin potential and prothrombin fragment 1+2 concentration were similar between patients with a more severe and a milder phenotype of severe haemophilia.

Von Willebrand factor (VWF)

Elevated VWF levels have been associated with thrombotic events in several prospective studies of patients with cardiovascular disease and thrombosis (30-33).

In contrast to what seems biologically plausible, Von Willebrand factor antigen was 1.6-fold higher among 8 severe haemophilia patients with a severe phenotype as compared to 10 patients with a milder phenotype; Von Willebrand factor activities were similar (15).

Other hemostatic factors

Fibrinolytic system

The fibrinolytic system is activated by the conversion of plasminogen to plasmin by tissue plasminogen activator (TPA) and urokinase. Plasminogen activators are administered in cardiovascular disease to prevent the sequelae of myocardial infarction. It has been suggested that hyperfibrinolysis may be associated with a more severe phenotype of severe haemophilia (34).

Grünewald et al compared fibrinolytic factors and activation markers of the fibrinolytic systems between severe haemophilia patients with a more severe and milder bleeding pattern. Statistically significant differences were reported for tissue-type plasminogen activator (TPA) and thrombin activatable fibrinolysis inhibitor (TAFI), not for plasminogen, plasmin inhibitor, plasminogen activator inhibitor type 1 (PAI 1), D-dimer, plasminplasmininhibitor complexes and TPA-PAI 1-complexes. The authors assume that increased stimulation of the fibrinolytic system is associated with a more severe phenotype. They hypothesise that ineffective haemophilic haemostasis in response to trauma evokes a protracted stimulation of the entire haemostatic system, including co-stimulation of fibrinolysis. The absence of coexistent congenital thrombophilia predisposes to excess stimulation of fibrinolysis, which cannot be down regulated effectively due to the dysfunctional intrinsic pathway.

Homocysteine

Hyperhomocysteinemia apart from the MTHFR mutation has hot been reported in association with variation in phenotype.

Discussion

There is ample evidence to show that the clinical phenotype of severe haemophilia may vary markedly among patients. A limited number of recent studies has suggested that prothrombotic factors may modulate the severity of severe haemophilia A (8).

Our review of the literature shows the most consistent findings for the factor V Leiden mutation. In two of seven studies, FVL was studied together with other prothrombotic factors and conclusions were drawn for the combination of prothrombotic factors (14, 15). Since different sets of prothrombotic factors were studied, it is not possible to perform a meta-analysis. Table 2 gives an overview of findings on determinants of clinical phenotype. Both factor V Leiden and the MTHFR C677T variant in the homozygous form may mitigate the severity of severe haemophilia.

No differences were found in the distribution of the PT G20210A mutation, in protein C deficiency, in protein S defi-

Table 2: Overview of findings.

		Most studies no association	Most studies association	Association when combined with other prothrombotic factors
Genetic factors	FVL		+	+
	PT G20210A mutation	x		+
	MTHFR C677T mutation		+	+
Plasma factors	low antithrombin	x		+
	low protein C	x		+
	low protein S	x		+
	hyperfibrinolysis		-	-

+ = decrease in severity of severe haemophilia
- = increase in severity of severe haemophilia
x = no specific association

ciency, in antithrombin, or in thrombin generation among severe haemophilia patients with or without a milder clinical phenotype. VWF antigens were higher in patients with severe phenotype compared to patients with non-severe phenotype, while VWF activity was similar (15). Few studies addressed the effects of fibrinolysis. Coagulation and fibrinolysis are linked processes. If thrombin generation is impaired, a less effective down regulation of fibrinolysis is expected. Mosier et al conclude that haemophilia A is a triple defect: reduced thrombin formation via the extrinsic pathway at low tissue factor concentrations, a reduced secondary burst of thrombin generation via the intrinsic pathway, and a defective down regulation of the fibrinolytic system by the intrinsic pathway (34). Dysfunction of fibrinolysis has been described in haemophilia (15, 34), and the absence of a prothrombotic factor predisposes to hyperstimulation of fibrinolysis (15). TAFI and TPA concentrations differed between patients with a milder phenotype and patients with a more severe phenotype (15). The correlation of TAFI-levels in plasma and clinical phenotype of severe haemophilia was not confirmed by Mosnier et al (34).

Although seven studies were identified, little or no definite conclusions could be drawn. Most published studies had a limited number of patients. Furthermore, the designs of the studies differed in selection of patients and in prothrombotic factors studied.

Known thrombophilic factors are rare, FVL occurs in 2-7% of a number of populations (35-37), the prothombin 20210A mutation occurs in 6.5% of the Spanish population (38) and the homozygous MTHFR mutation occurs in 5-12% of the population (24, 25, 39, 40), while about 10% of severe haemophilia patients have a milder clinical phenotype. The importance of known and unknown thrombophilic factors and possibly of non-random linkage of haemophilia and thrombophilic factors needs to be established.

Despite general recognition of considerable differences in severity of the clinical phenotype of severe haemophilia, there are no clear established criteria to distinguish mild patients from the ones with a more severe phenotype. Age at first joint bleed is increasingly recognised as an indicator of severity of severe haemophilia in children. Since weekly dose of prophylaxis and annual joint bleed frequency tend to stabilise in adolescence, these indicators could be used to distinguish adolescents with a milder clinical phenotype of severe haemophilia (41). Patients for whom prophylaxis was not available in the early years of life, may be selected on the basis of presence or absence of joint damage using the radiological joint score for haemophilic arthropathy according to Pettersson (42).

Phenotype of severe haemophilia depends on both genetic and environmental factors (including treatment) and their interactions (43). It seems likely that genetic and environmental factors act primarily by their effects on clot formation and lysis.

A promising tool for future research on determinants of variation in phenotype is real-time whole blood clot formation profiles by thromboelastography (44). In addition to plasma levels of prothrombotic factors and genetic prothrombotic factors, the defect in the factor VIII gene itself could be of importance for the clinical phenotype. Since patients with an inversion are unlikely to have any factor VIII, these could be more severe patients. Also, clearance of factor VIII should be considered, since patients with a longer half-life of factor VIII could be the patients with a milder clinical pattern.

Clinical phenotype may also be influenced by factors other than those involved in clot formation and lysis. Patients with a less intensive inflammatory response in cartilage could have less arthropathy and therefore a milder clinical phenotype (45).

Muscle training (46) and physical intensity of work also influence phenotypes of severe haemophilia.

In conclusion, the FVL mutation is the factor that most consistently appears to decrease severity of severe haemophilia. Findings on other thrombophilic factors are inconclusive. There is a need for research on potential determinants of phenotypes of severe haemophilia in order to individualise the treatment of severe haemophilia.

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