High factor VIII and the risk of venous thromboembolism

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Summary
There is now convincing evidence that a high level of coagulation factor VIII is an important risk factor for venous thromboembolism. A factor VIII plasma concentration above 1500 IU/l is associated with an almost 5-fold risk for a first episode of venous thrombosis. In thrombosis patients high factor VIII has been shown to persist over time and is not related to an acute phase reaction. High factor VIII is also an important risk factor for recurrence of venous thrombosis. In a prospective cohort study factor VIII levels exceeding the 90th percentile of the patient population conferred an almost 7-fold risk of recurrent venous thrombosis. The pathomechanisms leading to venous thrombosis in patients with high factor VIII are still unclear. In many patients, however, a biochemically detectable hypercoagulable state (as represented by elevated levels of the coagulation activation marker prothrombin thrombin fragment F1.2) was demonstrated. The optimal duration of secondary thromboprophylaxis for patients with high factor VIII levels is uncertain. We currently perform an interventional trial comparing conventional to extended anticoagulation. Reduction of factor VIII by administration of a non-selective β-receptor blocker might be a promising therapeutic concept which is currently under investigation.

V enous thrombosis is a frequent disease with an incidence of 1 or 2% per year. Over recent years, considerable progress has been achieved with regard to elucidating the mechanisms leading to clot formation within the venous system. Most importantly, several new congenital and/or acquired risk factors were detected. The prevalence of these risk factors among patients with venous thrombosis is high and ranges between 5 and 30%. This implicates that many patients with venous thrombosis carry at least more than one of them. There is also strong evidence that the increase in the risk associated with compound clotting abnormalities is multiplicative rather than additive as compared with the risk associated with single defects.

Besides mutations in genes encoding for coagulation factors V (G1691A; factor V Leiden) and II (G20210A), the lupus anticoagulant and hyperhomocysteinaemia, high levels of several coagulation factors (factor VIII, IX and XI) belong to the most important “new” risk factors of venous thrombosis.

High factor VIII concentration and the risk for a first episode of venous thrombosis

In 1995, Koster and colleagues reported that a factor VIII concentration higher than 1500 IU/l confers an almost 5-fold risk for a first episode of venous thrombosis (1). The risk of thrombosis associated with high factor VIII was independent of blood group and von Willebrand factor levels. The prevalence of factor VIII concentrations >1500 IU/l among thrombosis patients enrolled in this study was as high as 25%. Adjustment for fibrinogen – an indicator of an acute phase reaction – did not substantially affect the risk of thrombosis conferred by high factor VIII concentration supporting the concept that high factor VIII concentration is the cause rather than the consequence of venous thrombosis.

The finding that a high plasma concentration of factor VIII is a major risk factor for venous thrombosis is promising therapeutic concept which is currently under investigation.
for venous thrombosis was subsequently confirmed in several studies. In 1997, O’Donnell and colleagues reported that elevated factor VIII (>1000 IU/l) emerged as the single most common clotting abnormality among 260 thrombosis patients with a prevalence of more than 25% (10). Only a very few patients had a biochemically detectable acute phase reaction as indicated by elevation of ESR (10), fibrinogen or C-reactive protein.

Kraaijenhagen and colleagues reported that the risk for a single episode of venous thrombosis increased by 10% for each 10 IU/dl increase in factor VIII. In this retrospective study, high factor VIII concentration was also associated with an increased risk of recurrence of venous thromboembolism (3). Factor VIII was re-determined several years after the first measurement in a subset of patients. It turned out that high plasma levels of factor VIII were very consistent over time (r = 0.8, p = 0.01). Again, the data were similar after adjustment for fibrinogen and C reactive protein thereby excluding an acute phase reaction as the cause for elevated factor VIII levels (4). Furthermore, they concluded that increased factor VIII level following venous thrombosis is persistent and independent of an acute phase reaction.

The risk of venous thrombosis is not only dependent on the severity of risk factors but also on their number. This contention holds true also for thrombosis patients with high factor VIII concentration. Lenssen and colleagues investigated the contribution of high factor VIII levels to the risk of thrombosis among family members with factor V Leiden (6). They found in selected families as well as in unselected families higher incidence rates and a higher odds ratios among individuals harbouring both defects (factor V Leiden and factor VIII levels >150 IU/dl) as compared with those without an abnormality or individuals carrying only one risk factor.

### High factor VIII level and the risk for a recurrent episode of venous thrombosis

In 1992, we initiated a prospective cohort study (Austrian Study on Recurrent Venous Thromboembolism, AUREC) with the aim to investigate the incidence of recurrent venous thrombosis, to identify risk factor for recurrent venous thromboembolism and to characterize subgroups of patients with a particular high (or low) risk of recurrence. In the frame of this study, we measured factor VIII coagulant activity in 360 patients with a first episode of spontaneous venous thromboembolism approximately 3 weeks after discontinuation of oral anticoagulant therapy (5). We then prospectively followed the patients for a mean observation period of 30 months. Recurrent venous thromboembolism was seen in 38 patients (10.6%). Patients with recurrent venous thromboembolism had higher factor VIII levels than those without recurrence (182 ± 66 vs. 157 ± 54 IU/dl, p = 0.009). When factor VIII was entered as a continuous variable in a Cox proportional hazard model, the relative risk of recurrence was 1.08 (95% confidence interval 1.04 to 1.12; p <0.001) for each 10 IU/dl increase in factor VIII. After adjustment for age, sex, factor V Leiden, the prothrombin G20210A mutation and duration of oral anticoagulation, factor VIII remained a strong and independent risk factor (relative risk 1.07, 95% confidence interval 1.02 to 1.12; p = 0.001).

The aforementioned analysis assumed a graded relationship between levels of factor VIII and the risk of recurrence. To evaluate whether this relationship was linear or whether there was a threshold in the risk of recurrence with regard to the factor VIII level, we calculated the relative risk for different factor VIII ranges. Compared to the reference range (first quartile), an increased risk was seen for patients with factor VIII levels exceeding the 90th percentile. These patients had an almost 7-fold higher risk of recurrence than those in the reference group. The relationship between high factor VIII and the risk of recurrence was even stronger after adjustment for age, sex, factor V Leiden, the factor II G20210A mutation and duration (Fig. 1).

We next investigated the contribution of high factor IX level (defined as a factor IX clotting activity >138 IU/dl) to the risk of recurrent venous thromboembolism conferred by high factor VIII levels (11). We found that the risk of recurrence (compared with the reference group with low factor IX and low factor VIII) was highest among patients with both high factor IX and high factor VIII (relative risk 6.6 with a 90% confidence interval of 3-15) as compared with patients with high factor VIII and low factor IX (2.7, 0.9-7.8) or with
those with low factor VIII and high factor IX (relative risk 1.5 with a confidence interval of 0.8-2.7) (Tab. 1).

Our findings are in accordance with the concept that venous thrombosis is a multi-causal disease which depends on the interaction of acquired and/or hereditary risk factors.

**Mechanism(s) leading to high factor VIII and development of thrombosis**

The cause of high factor VIII in patients with venous thromboembolism is unknown. An investigation of the promoter and the 3’-terminus of the factor VIII gene for possible polymorphism associated with raised factor VIII antigen level in a cohort of more than 60 individuals with a thrombotic tendency was without success (7). Up to date convincing data that would indicate hereditability of high factor VIII level are not published.

A biochemically detectable hypercoagulable state – as represented by elevated levels of the coagulation activation marker prothrombin fragment F 1.2 (F1.2) – was found in the majority of thrombosis patients with a high factor VIII level (9). We measured F1.2 and thrombin antithrombin complexes (TAT) in venous blood and in blood emerging from a standardized injury of the microvasculature (made to determine template bleeding time) of patients with a high factor VIII level (9). We found in the majority of thrombosis patients with a high factor VIII level (9). We found high levels of vasopressin in patients with venous thromboembolism, and an elevated factor VIII level.

Recently, Kraaijenhagen and colleagues found high levels of vasopressin in patients with venous thrombosis and high factor VIII level (2). In these patients, administration of a non-selective β-receptor blocker (propranolol) resulted in a significant reduction of both vasopressin plasma concentrations and factor VIII levels. In patients with high factor VIII and venous thrombosis, non-selective β-receptor blockade appears to be a promising therapeutic concept as the potential side effects of this treatment modality are expected to be minimal when compared with the rate of complications associated with alternative treatment options. However, further studies are mandatory before a general recommendation can be given.

**Potential treatment modalities for patients with high factor VIII and venous thromboembolism**

The optimal duration of secondary thromboprophylaxis for patients with venous thromboembolism entails balancing the risk of recurrence after discontinuation of oral anticoagulation and the risk of bleeding during anticoagulation (4). Patients with a high risk of recurrent thrombosis such as patients with antithrombin deficiency, malignancy or the lupus anticoagulant are candidates for extended secondary thromboprophylaxis. In these patients the risk of bleeding conferred by anticoagulation is most probably outweighed by the risk of recurrence after discontinuation of anticoagulation. With regard to the patients with high factor VIII, it is unclear whether this subset of thrombosis patients benefits from extended oral anticoagulant therapy. In order to further investigate this issue, we currently perform an interventional trial in patients with a first episode of spontaneous venous thrombosis and high factor VIII comparing standard treatment (i.e. oral anticoagulation for six months) to extended secondary thromboprophylaxis. Until data from this trial are at hand, prolonged anticoagulation cannot be recommended for patients with a first episode of spontaneous venous thromboembolism and an elevated factor VIII level.

References

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