Inhibitor development in nonsevere hemophilia A
Eckhardt, C.L.

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Chapter 1

General introduction and outline of the thesis

C.L. Eckhardt, K. Fijnvandraat
Chapter 1

**GENERAL INTRODUCTION AND OUTLINE OF THE THESIS**

**What is hemophilia A and how is it treated?**

Hemophilia A is an X-linked inherited bleeding disorder that affects approximately 1 in 5,000 male live births. It is caused by a deficient plasma level of clotting factor VIII. Factor VIII is an essential protein in the blood coagulation and circulates in an inactive form bound to von Willebrand factor, that protects it from proteolytic degradation. In response to injury, factor VIII is activated by thrombin and separated from von Willebrand factor. Factor VIII serves as a cofactor for factor IXa and contributes to hemostasis by enhancement of thrombin generation and propagation of fibrin formation. Factor VIII deficiency results in suboptimal thrombin generation and fragile blood clots that easily bleed.

In healthy individuals normal factor VIII plasma levels (FVIII:c) range from 50 to 150 International Units per deciliter (IU dL⁻¹). Factor VIII is encoded by the factor VIII gene (F8), mutations in this gene result in hemophilia A. Over 2,000 different mutations in F8 have been described to cause hemophilia A and are registered in online databases. Large mutations cause a complete absence of factor VIII in the circulation (FVIII:c, <1 IU dL⁻¹), whereas most missense mutations lead to decreased factor VIII plasma levels (FVIII:c, 2-40 IU dL⁻¹). Hemophilia A manifests as a mild, moderate or severe bleeding disorder, depending on the plasma level of factor VIII. Patients with severe hemophilia A have no measurable factor VIII levels (FVIII:c, <1 IU dL⁻¹) resulting in spontaneous bleeds in joints and muscles, whereas moderate hemophilia A patients (FVIII:c, 1-5 IU dL⁻¹) usually only bleed after minor trauma and mild hemophilia A patients only after major trauma or surgery. About half of the patients have a nonsevere form.

Bleedings can be treated or prevented by intravenous administration of factor VIII concentrates. In the late 1950s and most of the 1960s, hemophilia A patients were treated with whole blood or plasma, containing very low levels of factor VIII. A great advancement came in the mid-1960s when substitution therapy became available for the first time in a more concentrated form: cryoprecipitate. By the late 1960s methods to purify factor VIII from pooled donor plasma became available, resulting in the first factor VIII concentrates. In the early 1980s a devastating complication of the production of factor VIII concentrates from large plasma pools became apparent when they were discovered to transmit blood-borne viruses, including human immunodeficiency virus (HIV) and hepatitis B and C. Large numbers of patients with hemophilia A were infected with HIV and hepatitis B and C. Tragically, as a consequence of the sequelae of these diseases many hemophilia patients died. To improve the safety of factor VIII concentrates viral inactivation procedures were introduced. Nowadays plasma derived factor VIII concentrates can be regarded as safe with respect to viral transmissions. The successful cloning of F8 in 1984 was a major breakthrough in the treatment of hemophilia A, as it enabled the development of factor
VIII concentrates by recombinant-DNA techniques. Promising new recombinant products with prolonged half-lives (normally 8-12 hours) are being tested in clinical trials. Treatment with factor VIII concentrates is very expensive (annual cost for an adult patient with severe hemophilia A is about € 200,000.-) and only available for ~25% of the hemophilia A patients worldwide.

In severe hemophilia A regular prophylactic infusions with factor VIII concentrates are required (one to three times a week) to prevent spontaneous bleeds and preserve normal joint an musculoskeletal function. Mild and most moderate hemophilia A patients generally only need therapeutic factor VIII concentrates on demand because of a mild bleeding phenotype. A cheap and safe alternative to achieve hemostatic factor VIII levels in mild patients is desmopressin (1-deamino[8-D arginine]-vasopressin, DDAVP). Desmopressin increases endogenous factor VIII levels two- to six fold by release of von Willebrand factor from endothelial cells. For minor bleeds or small interventions the treatment of desmopressin is therefore preferred. In patients with mild hemophilia A treatment with factor VIII concentrates is reserved for large bleeds or surgery. In those clinical circumstances a higher and more prolonged increase of factor VIII plasma levels is required, that can not be obtained by the use of desmopressin. In this thesis patients with mild and moderate hemophilia A will be regarded as one group: nonsevere hemophilia A. As the genetic background, the phenotype (presence of circulating endogenous factor VIII) and the treatment strategy are comparable in these patients.

Inhibitor development: a severe complication of treatment

A severe complication of the treatment with factor VIII concentrates is the development of inhibiting antibodies against factor VIII, also called inhibitors. Inhibitors challenge the treatment of hemophilia A as they inactivate factor VIII that is administrated for treatment or prevention of bleeding episodes. The development of inhibitors is elicited by exposure to therapeutic factor VIII. In severe hemophilia A patients it occurs in approximately 30% of the patients, usually during childhood within the first 50 days of treatment. Because nonsevere hemophilia patients are less frequently exposed to therapeutic factor VIII and the presence of circulating endogenous factor VIII that may induce tolerance, inhibitor development is less common in these patients. However, when inhibitor development does occur in these patients the clinical impact may be profound. In the majority of these patients the inhibitor neutralizes endogenous factor VIII, reducing the factor VIII plasma level below 1 IU dL^{-1}. This is accompanied by spontaneous and major bleeding complications.

In severe hemophilia A, the elimination of inhibitors is classically attempted by repeated high doses of factor VIII concentrates, a regimen called Immune Tolerance Induction or ITI. This treatment requires large amounts of factor VIII concentrate and is very expensive. It is only successful in 53-79% of the patients with severe hemophilia A.
optimal therapeutic approach to eradicate inhibitors in nonsevere patients are extremely scarce. To gain adequate hemostasis during bleeding episodes in inhibitor patients, the administration of factor VIII bypassing agents (activated prothrombin complex concentrate or recombinant factor VIIa) is required, with varying efficacy in achieving a satisfactory state of hemostasis. Consequently, inhibitor development is associated with increased morbidity, mortality and high costs-of-care.

Identification of patients with an increased risk for inhibitors will allow clinicians to implement preventive measures to lower the risk. Several genetic and environmental factors have been found to affect the inhibitor risk of patients with severe hemophilia A (Figure 1). The genetic risk is primarily determined by the mutation in the F8 gene, with the highest risk for large deletions, inversions and nonsense mutations. Other genetic risk factors include family history of inhibitors, ethnicity and genetic variation of immunoregulatory genes. Environmental risk factors that increase the risk for inhibitors are mainly related to the treatment regimen and include factor VIII product, reason for treatment and intensity of treatment.

Until now, most of the inhibitor research has focused on severe hemophilia A, whereas little is known about the etiology and outcome of inhibitor development in nonsevere hemophilia A. As nonsevere hemophilia A patients differ substantially from severe patients, both in genetic background and the treatment strategy, it is important to address the etiology and outcome of inhibitor development in these patients separately.

AIMS OF THE THESIS

The aim of this thesis is to gain further insight in the etiology and outcome of inhibitor development in nonsevere hemophilia A. The objectives are to study:

1. Genetic risk factors for inhibitor development in hemophilia A;
2. Environmental risk factors for inhibitor development in hemophilia A; and
3. The outcome of inhibitor development in nonsevere hemophilia A.

OUTLINE OF THE THESIS

This thesis consists of three parts involving the role of genetic and environmental risk factors for inhibitor development and the outcome of inhibitor development in nonsevere hemophilia A.

Part I focuses on the genetic risk factors for inhibitor development. In chapter 2 the role of the F8 gene mutation on inhibitor risk is assessed in a large international cohort of nonsevere hemophilia patients. Chapter 3 describes the association between genetic
General introduction and outline of the thesis

Figure 1. Known and potential genetic and environmental risk factors for inhibitor development variation of Fc receptors for IgG (Fc gamma receptors) and inhibitor development in a cohort of brother pairs with severe hemophilia A.

Part II addresses environmental risk factors for inhibitor development. Chapter 4 evaluates risk factors for inhibitor development in a single center cohort of nonsevere hemophilia patients. Chapter 5 describes the results of a prospective multicenter study which was aimed to determine the incidence of inhibitor development after intensive factor VIII replacement therapy for surgical procedures in patients with nonsevere hemophilia A. In chapter 6, the published studies on the association between surgery and inhibitor development were systematically reviewed and critically appraised.

Part III of this thesis concerns the outcome of inhibitor development in nonsevere hemophilia A. In chapter 7 the outcome of inhibitor development according to specific eradication strategies is described in 107 nonsevere hemophilia A patients with inhibitors. Chapter 8 describes the influence of inhibitors on mortality between 1980-2011 in a large international cohort of nonsevere hemophilia A patients.

The results of part I and part II of the thesis are discussed in chapter 9 and chapter 10, respectively. Chapter 11 provides the summary and the overall discussion and interpretation of the thesis.
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