Chapter 1

General introduction
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Hemophilia

Hemophilia is a hereditary clotting disorder which is caused by a deficiency of factor VIII (hemophilia A) or IX (hemophilia B). In the Netherlands the prevalence is around 10 per 100,000, resulting in about 1600 patients. The severity of the disease is determined by the residual clotting factor activity. Patients with mild hemophilia (>0.05-0.40 IU/ml) show little spontaneous bleeding and bleed excessively only after major trauma; patients with moderate hemophilia (0.01-0.05 IU/ml) may show excessive hemorrhages after minor trauma, while severe hemophilia (<0.01 IU/ml) is characterized by major bleeding occurring spontaneously or after minor trauma. Frequent bleeding in joints results into damage of the synovial tissue and arthropathy. Hemophilia is a genetic recessive X-linked trait and therefore patients are mostly men. Female family members can be carriers of the disorder, which is characterized by a 25% chance of having a son with hemophilia, and a decreased clotting factor activity level.

History

Although effective treatment has only become available in the recent decades, hemophilia was known to the ancient world. The earliest written references to what appears to be hemophilia are encountered in Jewish texts of the second century AD. Rabbinical rulings exempted male boys from circumcision if two previous brothers had died of bleeding after the procedure. The first modern description of hemophilia is attributed to Dr John Conrad, who clearly appreciated the three cardinal features of hemophilia: an inherited tendency of males to bleed. However, the first use of the word "hemophilia" appears in an account of the condition written in 1828 by Hopff (Über die haemophilie oder die erbliche Anlage zu tödliche blutungen). Hemophilia is sometimes referred to as "the royal disease" because several
members of royal families in Europe were affected by it. Queen Victoria had no ancestors with the condition but soon after the birth of her eighth child, Leopold in 1853 it became evident that he had hemophilia. Two of Queen Victoria's daughters were also carriers of hemophilia. The condition was transmitted through them to several Royal families. Perhaps the most famous affected individual was the son of Tsar Nicolas II of Russia, Tsarevich Alexis, who was born in 1904.

**Treatment and complications**

Many reputable scientist claimed early success in treatment with unusual substances. As recently as 1964 a report in Lancet claimed that peanut flour was effective for the treatment of hemophilia. The first hint of success came from Dr R.G. Macfarlane in 1934, who discovered that snake venom could accelerate the clotting of hemophilic blood. Plasma derived factor VIII and IX preparations became available in the early 1960s. Ever since the discovery by Dr Judith Pool of cryoprecipitate, replacement therapy with factor concentrates has been the most important component of hemophilia care. This treatment rapidly improved the medical and social situation of patients with hemophilia and considerably increased life expectancy.

In the early 1980s major side-effects became manifest when many patients became infected with the human immunodeficiency virus (HIV). Moreover, of all patients treated before 1992 with plasma-derived clotting factor preparations, 80 percent became infected with hepatitis viruses. Today, clotting factor preparations are virtually safe regarding blood-borne viruses, and the risk of hepatitis and HIV transmission must be considered negligible, whereas the development of neutralizing antibodies (‘inhibitors’) against the infused factor VIII or IX is an important issue.

The characterisation and cloning of the factor VIII gene in 1984 led to the availability of recombinant factor VIII a decade later. The availability of products that are not made from
human blood and therefore even theoretically incapable of transmitting human blood-borne pathogens, has further stimulated the use of prophylactic treatment. In the Netherlands since the late 1970s treatment of hemophilia has consisted of the intravenous infusion of clotting factor concentrates performed either on demand (at the moment of bleeding) or prophylactically. Prophylactic treatment is primarily prescribed to patients with severe hemophilia. The rationale for prophylaxis in hemophilia is that patients with a factor level of 0.01-0.04 IU/ml rarely develop chronic joint changes. By maintaining the plasma concentration of clotting factors at a level above 0.01 IU/ml hemophilia can be converted from a severe to a milder form\textsuperscript{15-17}.

Outline of this thesis

The main aim of this thesis was to study the effects of hemophilia treatment on both the medical situation and social functioning of hemophilia patients. Effective treatment of hemophilia has been available since the late 1960s\textsuperscript{7} and offered patients better prognosis but also had a large negative impact through blood-borne viruses. This has been described in Chapter 2. In Chapter 2.2 we studied mortality, causes of death and life expectancy in Dutch hemophilia patients between 1992 and 2001. With this study we complete the inventory of mortality in patients with hemophilia over thirty years, describing the period before\textsuperscript{18}, during\textsuperscript{19} and after the use of potentially contaminated clotting products. In chapter 2.2 the results of the Hemophilia in the Netherlands-5 (HiN-5) project are described and data are compared to the previous surveys. This chapter focuses on both medical issues, such as haemorrhages and joint problems but also on social aspects such as absence from work and school. Social functioning and health related quality of life of hemophilia patients compared to the general population are described in Chapter 2.3. In Chapter 2.4 clinical characteristics of hepatitis C positive patients are evaluated. Recombinant clotting factor preparations were
introduced in the early 1990s. Despite the serious side effects of plasma-derived clotting products these new products were not accepted as quickly as expected. In Chapter 2.5 factors influencing the use of recombinant factor VIII were studied.

Female relatives of male patients can be carriers of hemophilia; besides its impact on family planning carriership of hemophilia may also lead to bleeding problems. Chapter 3 evaluates whether carriers of hemophilia have more bleeding problems than to non-carriers, with a focus on specific risk-enhancing factors.
References


