Growing up with hemophilia
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Chapter 1

General introduction
Introduction

St. Petersburg, August 12 1904, Alexei Nikolaevich, Tsarevich of Russia and great grandson of Queen Victoria of England, is born with hemophilia ‘the Royal Disease’. His mother, Alexandra, was a carrier of the hemophilia gene. Alexei’s hemophilia was so severe that minor injuries, such as a cut, bruise or nosebleed, were potentially life-threatening. The nature of his illness was kept a state secret. Two navy sailors were assigned to monitor and supervise Alexei to prevent injuries, which were unavoidable nevertheless. The sailors also carried him around when he was unable to walk. The monk Rasputin was summoned to use hypnosis to relieve Alexei’s pain, since medication was not available. Hypnosis was not only believed to relieve pain, but was also supposed to reduce or stop the boy’s bleeds. As well as being a source of constant worry to his parents, the recurring episodes of illness and long recoveries interfered greatly with Alexei’s education [1, 2].

About a century prior to Alexei’s birth, in 1803, John Conrad Otto published the first paper recognizing a bleeding disorder to primarily affect men, and run in certain families, calling the males ‘bleeders’ [3, 4]. In 1813, a paper was published in the New England Journal of Medicine stating that affected men could pass the trait for a bleeding disorder to their unaffected daughters, indicating that the inheritance was X-linked; affected men inherit the mutant gene from their carrier mothers [5]. In 1828, the term ‘hemorrhaphilia’, later shortened to ‘hemophilia’ (‘love of blood’), arose [4, 6, 7].

In the fifties of the last century, it was discovered that hemophilia was an inherited deficiency of clotting factor VIII (hemophilia A) or factor IX (hemophilia
B), leading to spontaneous and posttraumatic bleeds and causing irreversible severe musculoskeletal damage. In addition to the inherited component, about 30 percent of cases of hemophilia are caused by a spontaneous mutation [5]. Both clotting factor VIII and IX take part in the pathway of blood clotting and affected individuals have severe (<1% concentration of clotting factors in blood), moderate (1-5%) or mild (5-40%) forms of the disease. Hemophilia A has a prevalence of about 1 in 5000 male births, and hemophilia B about 1 in 30,000 [4, 5, 8]. It was not until 1937 that researchers from Harvard University found that the clotting defect could be corrected [9]. As a result, mid-20th century, people with hemophilia could be treated with whole blood or fresh plasma obtained from donors without clotting defects [10]. However, most people affected by severe hemophilia at that time still died in childhood or in early adulthood, because the concentration of clotting factor in these human products was not sufficient to stop severe bleeding [4, 10].

The current management of hemophilia actually started in the 1970s. It was found that the concentration of clotting factors in the blood increased when pooled plasma was infused, obtained from thousands of donors, leading to effective treatment of bleeds [5]. This treatment led to reduction of musculoskeletal damage and better physical functioning [4]. The fortunate position changed drastically in the early 1980s, when in some countries up to 60-70% of people with severe hemophilia became infected with hepatitis B/C, and/or the human immunodeficiency virus (HIV), transmitted by pooled plasma of many different donors [4, 11]. Since the 90’s, genetically engineered factor products were provided by rapid progress in DNA technology, which allowed the industrial production of factor VIII and IX [5, 10, 11]. These safe and effective products enabled ‘prophylactic treatment’ with clotting factor (treatment in order to prevent bleeding and joint damage), ultimately allowing patients to maintain a near normal lifestyle. These advances in treatment have narrowed the life expectancy gap between patients with hemophilia and the general population [12].

Had Alexei Nikolaevich been born about a century later, and for example in Western Europe, his life would have been completely different. Despite his
royal status, Alexei would not necessarily have been carried around by two sailors. Nor would he have been confined to weeks in bed after a joint bleed, but could have moved around independently. The few bleeds he would have had, could have been treated with safe engineered clotting factor products, in addition to his regular prophylaxis to prevent bleeds in the first place. This would have led him to be much less of a torment to his parents, and sailors for that matter. Also, Alexei would have been able to participate in regular education and to enjoy play time with his peers. In case he would have wanted to be an emperor of Russia, this would have been within his range of options.

Modern hemophilia management in the Netherlands
In the Netherlands, around 1600 patients are affected with hemophilia, of which approximately 400 are children. Nowadays, children growing up with hemophilia can participate in society, while being monitored closely. Children with severe hemophilia receive regular prophylaxis at the time of diagnosis or after the first few episodes of joint bleeding [10, 13]. This means an intravenous infusion of clotting factor at least twice or three times a week. In contrast, patients with non-severe hemophilia rarely bleed spontaneously. Bleeds in non-severe hemophilia patients occur mostly after trauma or surgical procedures, and patients with non-severe hemophilia are therefore treated on demand. Most of these patients experience no functional limitations at a younger age, but are still required to adhere to lifestyle adaptations [14].

The Netherlands is a privileged country with one of the highest degrees of available clotting factor and prophylactic treatment (76-100%) for patients with hemophilia [15]. In most countries, cost of treatment is the biggest barrier to prophylaxis. It is estimated that, at a price of $1 per unit of recombinant factor VIII, the cost of prophylaxis for a child with severe hemophilia weighing 50 kg could reach $300.000 per year [16, 17]. Fortunately, treatment of hemophilia is fully covered by insurance companies in the Netherlands [18].

Despite this favorable context, challenging complications of clotting factor treatment arise: the development of inhibitory alloantibodies (‘inhibitors’) against clotting factor VIII or factor IX after administration. In addition, repeated
venous access and central venous catheters (‘port a cath’) are not free from complications either, such as infections. Inhibitors are the largest challenge, and arise in approximately 25-30% of severe hemophilia A patients and in only 3-5% of hemophilia B patients. Inhibitors cause treatment with clotting factor to be ineffective, limiting patients’ access to a safe and effective standard of care and expose patients to an increased risk of morbidity and mortality [4, 10, 16, 19, 20].

Hemophilia is a complex disease to manage. Knowledge and experience is concentrated in six specialized Hemophilia Comprehensive Care Centers (HCCCs) in the country, of which the Emma Children’s Hospital/AMC in Amsterdam is the second largest [15, 21, 22]. The multidisciplinary team present at the Emma Children’s Hospital/AMC consists of three (part-time) pediatric hematologists, two pediatric hemophilia nurses, a pediatric psychologist, a social worker and a pediatric physiotherapist. Their focus is on supporting and equipping children and adolescents with hemophilia and their parents with as many skills as possible to lead an independent life with a high health related quality of life (HRQOL) and optimal psychosocial functioning. It requires more than the treatment of acute bleeding; attention to psychosocial functioning and HRQOL is needed as well since this can impact health and treatment [22]. Home prophylactic treatment is initiated after adequate theoretical and practical education, and training and can be started by parents with young children with adequate venous access [12, 23-25]. But, infusing one’s child means crossing a considerable psychological threshold and can be burdensome for parents [26]. Older children and teenagers usually learn to self-infuse, but it is important to train before puberty: adherence problems due to a lack of perceived need are common during puberty [25-27]. Consequently, the process of home treatment is complex, and adequate guidance from the HCCC is warranted. As a result, preventing and treating medical related stress and chronic complications, and achieving the highest HRQOL are the main goals of hemophilia management nowadays [28, 29]. The challenge is to empower patients to manage their circumstances and challenges autonomously [25, 28, 29]. While sharing the modus operandi of this extensive multidisciplinary team
could be beneficial to other HCCCs, a proper overview could be beneficial to be used in the development of intervention programs.

Health related quality of life
Due to advances in medicine, more children with chronic health conditions are able to grow up as adults. While this is a great step forward, it increases the number of children living with the long-term consequences of chronic health conditions and compounds the impact on their HRQOL problems over their lifespan [30]. HRQOL is a multidimensional concept that refers to the impact of health and illness on an individual’s quality of life (QOL), which encompasses not only physical aspects but also social and emotional elements [31, 32]. The endorsement of the importance of these aspects has led to the development of instruments designed to measure HRQOL [33-35]. The evaluation of HRQOL is essential for a full understanding of the influence of a health condition on an individual and to evaluate the impact of different treatment strategies [36].

How to measure HRQOL
HRQOL is subjective by definition, because an individual’s perception will define the impact on the person’s life. For example, an identical health condition may result in different ratings of HRQOL in different individuals. As a consequence, the patient’s report is the best source of information about what he or she is experiencing when measuring HRQOL [37]. Thus, HRQOL assessment should be a form of a patient reported outcome (PRO); a PRO is any report of the status of a patient’s health condition that comes directly from the patient, without interference by anyone else [38]. At first, clinicians believed that children’s self-reported health information was unreliable, which resulted in the underuse of PROs in pediatrics [39]. But, research showed that children over the age of 7 years are able to reliably report their HRQOL [40].

Measuring HRQOL in children poses several challenges. First of all, measuring HRQOL starts with the choice of an adequate HRQOL instrument. In general, there are two types of HRQOL instruments: generic and disease-specific. Generic HRQOL instruments provide the possibility to compare children
across different chronic health conditions and to compare them to the healthy-or general population [30, 40-42]. Disease-specific measures on the other hand, can provide a detailed or reliable measurement of dimensions that are specific to a certain condition and are usually more sensitive to the impact of changes in clinical conditions or treatment on HRQOL [31, 43, 44]. Even though generic HRQOL instruments have been used most frequently, a combination of the two types of measures may provide the optimal information [30, 31, 45]. For children and adults with hemophilia, several age and disease-specific HRQOL instruments have been developed [46-49]. However, up to date it is not clear which HRQOL instrument is most optimal for use in hemophilia.

To be able to measure HRQOL over time in children growing up from adolescence into (young) adulthood, appropriate instruments and normative data are needed [41, 50]. Literature strongly recommends using the same mode of administration when comparing groups or changes over time [51]. In the Netherlands, no HRQOL instruments are available to measure HRQOL from early childhood into adulthood. With the aim to study children and YA with chronic health conditions over time, and for use in clinical practice, norm data have become indispensable [32].

**Explaining HRQOL and psychosocial problems**

When looking at all the aspects of living with a chronic condition - one can imagine that this has a major influence on children and their families. Many studies show that children with a chronic health condition, and their mothers in particular, are at increased risk for psychosocial problems or lower quality of life compared to healthy peers [52, 53]. However, how people react to and cope with stressors is not set in stone. Several previously developed theoretical models have hypothesized that there are different factors that are related to a chronic health condition that may impact children’s emotional, behavioral, and social functioning and HRQOL [52, 54]. Wallander & Varni (1992) have combined so-called ‘risk’ and ‘protective’ factors into a model to be able to explain why some people develop psychosocial problems related to chronic conditions and others do not; the ‘disability-stress-coping model’ (see Figure 1).
By identifying risk and protective factors, which respectively negatively or positively influence psychosocial adjustment, psychosocial support for children and their families can be delivered [52]. Risk factors include illness-related stressors (e.g. diagnosis, severity), and psychosocial stressors (e.g. restrictions, treatment). Protective factors on the other hand, include personal factors (e.g. competence, self-esteem), family factors (e.g. parental distress) and stress processing factors (knowledge, self-management) [52, 54]. The model shows links between illness-related stressors and HRQOL/psychosocial functioning, which are moderated by children's stress processing. Subsequently, this is influenced by personal and family risk- and protective factors [52, 54]. In sum, research is needed to identify which children and parents are at risk for developing problems or who are resilient in the adaptation process.

Fig. 1. Disability-stress-coping model of child adjustment to pediatric chronic illness by Wallander & Varni [54].

Living with hemophilia during childhood and adolescence
Children growing up with bleeding disorders nowadays experience the advances in medicine that have occurred over the past decades. In the Netherlands, boys with severe hemophilia receive prophylactic treatment to reduce the risk of irreversible joint damage. Despite the advantages of being able to provide care
at home (e.g. less hospital visits, more independence), the large responsibility for management of hemophilia, such as administration of treatment by intravenous infusion of clotting factor concentrate, is still burdensome [55, 56]. Moreover, children with hemophilia still endure difficulties and impairments, such as hospital visits, frequent injections and limited participation in (sport) activities [57]. To able to face such difficulties and impairments, adequate skills are required. As the model by Wallander & Varni shows (Figure 1), elements such as self-management and coping skills are important protective factors related to psychosocial outcomes [58].

HRQOL as an outcome has received increased attention in pediatrics over the past years [32, 33, 36, 41]. Literature on HRQOL of children with hemophilia is conflicting and is expected to vary between countries. Some suggest that hemophilia does not negatively affect HRQOL or psychosocial functioning during childhood [59], where other studies report that children with hemophilia do have a lower HRQOL compared to their healthy peers, particularly in children with severe disease [58, 60-62]. Understanding what it is like to grow up in ‘the golden era’ of hemophilia care is valuable in accommodating the needs and possibilities of children with hemophilia.

**Transition from childhood to adolescence and young adulthood**

For all children, transition into adulthood is a critical phase. Children go through several challenging transitional phases while growing up, such as achieving personal identities, gaining independence from parents, initiating employment and building significant relationships outside of their families [63]. Adolescents with chronic illnesses are expected to pass similar developmental stages as healthy peers, but often have a delay in their developmental trajectory [64]. This does not only affect patients with a chronic illness during adolescence, the consequences often remain in (young) adulthood and result in having more trouble finding employment, leaving the parental home, marrying, becoming parents and having lower income levels than healthy peers [65, 66].

Adolescents with hemophilia usually start with learning self-infusion around the age of eleven, a procedure which involves complex self-management
skills, and are confronted with the challenges in taking responsibility for their disease and its treatment [26, 67]. For example, compliance with prophylactic treatment frequently declines during teenage years, mostly due to the desire to be as others, leading to increased risk for complications and deterioration of the chronic health condition [68-70]. In addition, low self-management skills are an obstacle for optimal adherence to prophylaxis [71]. However, research has shown that the process of achieving complete self-management in adolescents and young adults (YA) with hemophilia is not reached until a median age of 22.6 years [67]. Therefore, it is recommended that the pediatric team promotes self-management underpinned by psychosocial care and support for children with hemophilia early, so that the transition process can be gradual [28, 72].

To fully understand what it means to grow up with hemophilia, it is valuable to include the perception of YA in research, using qualitative methods. Unfortunately, this is not common practice. Insight into the psychosocial development of YA with hemophilia helps to develop interventions in pediatric healthcare to create conditions for optimal participation in society. Loss of independence, the inability to achieve educational goals, and difficulty with employment, as can be experienced by patients with hemophilia, contribute to low self-esteem and low HRQOL [73]. To address these aspects, it is important to assess the psychosocial development and HRQOL of young adults with hemophilia.

Consequences for parents
As demonstrated earlier, a child with a chronic health condition can have a great impact on patients’ lives, but also on the whole family, especially parents. Research has shown that parents of children with a chronic health condition frequently report anxiety, depression, physical problems and cognitive problems and are more likely to experience greater levels of parental distress and lower HRQOL than parents of healthy children [52, 53, 74]. Also, Figure 1 showed that parental psychosocial stressors can negatively influence the well-being of the child [54].

Up to date, the psychosocial impact of hemophilia on parents has only
been addressed in a handful of studies, and results are quite ambiguous. When comparing parents of boys with hemophilia to other illness groups, parents of boys with hemophilia experience less impact of the disease on their quality of life and lower psychosocial strains than parents of children with other chronic health conditions, such as diabetes [75]. On the other hand, it has also been demonstrated that parents of boys with hemophilia are deeply affected by their child’s condition. Besides feelings of anxiety, helplessness, guilt and worry over their child’s condition, parents also report to be largely impacted by their child’s pain [76]. Especially mothers are at risk for psychosocial problems compared to fathers, because they are usually more involved in the daily care for their child [75]. Moreover, being a mother and carrier of hemophilia and having a child with hemophilia is reported to be life changing, and may come with feelings of guilt and anxiety [77]. Therefore, more insight into psychosocial functioning of mothers of boys with hemophilia in the Netherlands is important.

**Psychosocial support and interventions in hemophilia**

Over the past decades, the increased recognition of improving the adjustment to a chronic health condition has led to the development and evaluation of psychosocial interventions [78-80]. Generally, interventions for children with a chronic health condition have a psycho-educational nature, usually containing the training of coping skills and knowledge by cognitive behavioral therapy techniques [81, 82]. Interventions that provide emotional support (e.g. peer support), psycho-education, coping skills and symptom reduction are the most common type of interventions [78], and relate to important factors in the Wallander & Varni model (Figure 1) [52, 54]. Besides individual treatment, group interventions may be effective and interventions that include parents have gained interest as well [78, 79, 83].

A major challenge in supporting children with hemophilia and their parents, especially in developing countries, is a lack of access to a multidisciplinary team; a team that can provide contextualized, structured psycho-education programs and provide advice on hemophilia, recognizing bleeds, adherence, home management, care of the child and parental self-care [84]. We also
know that education on these topics significantly improves self-management, leading to less depression and anxiety levels in parents and improvement in HRQOL of children [85]. Therefore, offering educational programs to children and their families is of utmost importance [85-88]. Unfortunately, resources are scarce concerning the evidence-based efficacy of interventions that are available for children with hemophilia [89]. An example of an evidence-based tool which is being used at the HCCC in Amsterdam, is the KLIK system. KLIK is a web-based tool to monitor and screen HRQOL over time in children with chronic health conditions. This enables the detection of problems at an early stage that arise for individual patients, so tailored interventions can be offered before problems increase [90, 91]. Another example of an evidence-based intervention is the ‘On Track’ group course intervention program [92]. The course has a six weekly-program, with the aim to learn active coping skills, to promote resilience and to prevent psychosocial problems in children with chronic health conditions [83]. Furthermore, in Rotterdam an intervention was developed to increase adherence in children with hemophilia, by providing a period of transmural care by a hemophilia nurse. Although no improvement in adherence was observed, positive effects were found in communication and perceived support between parents and the HCCC [93]. Furthermore, healthcare providers can offer psychosocial support by helping patients and their families develop strategies to cope with physical, mental, emotional, and social challenges related to having a bleeding disorder. As we have seen before, HRQOL depends largely on the ability to adjust to having a chronic disorder and the challenging circumstances that may arise [28, 52].

**This thesis**

The unique process of growing up with hemophilia has been described in various ways. However, a comprehensive overview of living with hemophilia and its consequences across different domains and phases of life would be beneficial for a comprehensive understanding of this process. In order to describe HRQOL and psychosocial functioning as one of the main outcomes, adequate reliable and valid measures are required. Measures that are feasible
for use in research and clinical practice are important, to get insight into the impact of hemophilia on patients. With knowledge about these outcomes, adequate psychosocial support can be offered to patients and families.

This thesis adds to the current literature by focusing on the HRQOL and psychosocial functioning of children and young adults with hemophilia, and their parents, divided in three parts:
I. Development and evaluation of instruments
II. HRQOL and psychosocial outcomes
III. Psychosocial care provided to children and adolescents with hemophilia and their families

Aims of this thesis:
I. Development and evaluation of instruments:
   • To demonstrate the importance of measuring HRQOL in pediatric patients and its challenges.
   • To assess the methodological quality of studies on the psychometric properties of HRQOL instruments developed in patients with hemophilia.
   • To assess the reliability and validity of an instrument aiming to assess coping and perception in boys with hemophilia (8-12 years).
   • To validate and collect normative data for a generic HRQOL instrument for young adults (18-30 years).

II. HRQOL and psychosocial outcomes:
   • To assess the HRQOL of children and adolescents growing up with hemophilia.
   • To identify themes important in daily life for young adults with bleeding disorders.
   • To assess the HRQOL, developmental milestones and self-esteem in young adults with bleeding disorders.
   • To assess the psychosocial functioning of mothers of children with hemophilia.
III. *Psychosocial care*

- To describe the psychosocial care and interventions offered to children and adolescents with bleeding disorders and their parents in the Netherlands.

**Outline of the thesis**

The general introduction of this thesis is covered in *Chapter 1*. Part *one* of this thesis (chapters 2, 3, 4 and 5) covers the development and evaluation of HRQOL instruments. *Chapter 2* starts with a demonstration why it is important to measure HRQOL in pediatrics, and what challenges come with measuring it. We aim to provide an overview of the philosophy of and tools used in HRQOL research in children. In *Chapter 3*, we perform a systematic review on the measurement properties of HRQOL instruments developed in hemophilia. By critically appraising and comparing the measurement properties of HRQOL questionnaires studied in hemophilia, we provide a first solid step to select the best measurement instruments for hemophilia. *Chapter 4* describes the reliability, validity and evaluation of an instrument aiming to assess coping and perception in boys with hemophilia (8-12 years). *Chapter 5* reports on Dutch normative data of the PedsQL for young adults (PedsQL_YA) and assesses the reliability and validity of the PedsQL_YA in the general Dutch population.

The *second* part (chapters 6, 7, 8 and 9) of this thesis focuses on the HRQOL and psychosocial outcomes of children and young adults with hemophilia, and their mothers. First, *Chapter 6* describes the generic and disease-specific HRQOL of children growing up with bleeding disorders in comparison to their healthy and chronically ill peers and according to severity. *Chapter 7* follows by describing themes important in daily life for young adults with bleeding disorders, based on qualitative research (focus groups). With this information, appropriate instruments can be chosen and administered to address the daily functioning of young adults, which is done in *Chapter 8*. This chapter covers not only the HRQOL of young adults with hemophilia, but also their developmental milestones and self-esteem in comparison to (healthy) peers. *Chapter 9* describes the psychosocial functioning (anxiety, depression and parental distress) of mothers of children with hemophilia.
The third part of this thesis, Chapter 10, describes the psychosocial care and interventions provided to children and families by the multidisciplinary team of the HCCC at the Emma Children’s Hospital/AMC in Amsterdam.

Finally, this thesis ends with Chapter 11; a general discussion including a summary of the results, main findings, limitations, future perspectives and key messages.
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