Aging with haemophilia –

Medical and psychosocial impact

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Experiences from living with haemophilia
makes dealing with the aging process
less demanding.

Aging with haemophilia

Medical and psychosocial impact

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Van Creveldkliniek-Haematology

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Preface

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Introduction

Haemophilia is no longer a disorder of young children, adolescents and young adults. Thanks to prophylactic treatment life expectancy of haemophilia patients in the Western countries is increasing to almost normal. The haemophilia society is now dealing with a new category of patients: the seniors. These seniors were young at the time when no proper treatment for haemophilia existed. Since the 1960s haemophilia patients could receive intravenous factor VIII and IX replacement therapy prepared from plasma and subsequently more and more treatment and large pool clotting factor products became available. This implies that in their youths these men suffered from severe bleedings which caused permanent joint damage. On top of that a significant part of the Dutch haemophilia population was infected with HIV and/or HCV before the development of adequate viral inactivation of blood products in the 1990s.
At present these seniors with haemophilia not only have to live with premature arthropathy and HCV/HIV infection, they are also confronted with age-related ailments. Progressive arthritis and declining fitness may lead to an increasing dependency on medical treatment, a growing number of hospital visits, and loss of independency. In connection with the physical aspects of aging older patients may encounter psychosocial problems which may be triggered by early retirement, loss of health and altered family dynamics.

Up till now very little has been published about these problems although they are quite common. In this book several authors cover a variety of problems related to the aging process. The editors are grateful that colleagues from other haemophilia centres were willing to share their expertise and to contribute to this book.

This book aims at all health care professionals − medical , allied health and psycho-social specialists − dealing with haemophilia patients. People who are in regular contact with haemophiliacs and especially those who do not treat many patients, may gain a better insight in the specific complaints and the need of treatment modified to the special situation of the person with haemophilia. A list of practical recommendations on how to avoid complications for people with co-morbidity is added to the last chapter.

Utrecht, August 2007

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Chapter 1. Life expectancy and co-morbidity

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Changing perspectives for haemophilia

Until the early 1960s haemophilia was a life threatening disease that caused early death after a life of recurring painful bleedings, especially in patients with severe haemophilia. Treatment of bleedings consisted of bed rest, splints and icepacks. [photo] With the large scale introduction of clotting factor concentrates the lives of haemophilia patients have changed dramatically. However, this change for the better is still a privilege of patients in the Western world.

Nowadays a bleeding can be prevented by prophylactic infusion of clotting factor concentrates and whenever a bleeding does occur (extra) clotting factor concentrate can be used. As soon as home-treatment is possible, the patient or his family will be largely self-sufficient and less dependent on their doctor. Covered by clotting factor concentrates medical procedures may be performed without serious bleeding problems as well. Recurrent hospitalization in case of bleedings is no longer necessary, which has reduced absenteeism from school or work.

Since people with haemophilia are being treated adequately they reach the age of procreation. However, they may not be aware of the genetic consequences.(1) Haemophilia treaters should counsel for the heredity of haemophilia. They should stress the fact that daughters of a haemophiliac invariably will be carriers of the disease and that sons are healthy and cannot pass on the disease. Parents should also be aware that carrier-daughters have a 25% chance to have sons with haemophilia.

Due to extreme lyonisation some carriers have a decreased factor VIII or IX level with increased bleeding tendency. In all daughters of haemophilia patients clotting factor levels should be measured.(2,3) This should be done early in life. If decreased levels of clotting factors are found, both parents and daughter will know how to act in case of trauma, bleeding, pregnancy or medical intervention.

The risk of passing the haemophilia gene may be a burden for the haemophiliac and have a strong impact on his and his partner's view on procreation. He and his partner have to take a decision: do we want children, and if so do we accept the risk of passing the haemophilia gene to all our daughters. Being a carrier is not considered to be a disease, so in the Netherlands prenatal diagnosis and pre-implantation diagnostics to prevent the birth of haemophilia carriers is not done routinely. Donor insemination and adoption are the only ways to prevent the birth of a carrier daughter. To support parents during the phase of decision making, adequate genetic counselling and psycho-social support is important. This should be initiated at the haemophilia centre, preferably in co-operation with the department of clinical genetics.

Life expectancy of Dutch haemophilia patients

The improved treatment changed the haemophiliac's life not only medically, but also socially. Both life expectancy and quality of life have improved especially for those who escaped infection with HIV and/or HCV. However, a considerable number of older patients has been infected by these viruses transmitted through unsafe clotting factor concentrates. Between

1979 and 1985 patients were infected with HIV. Infection rates for HIV in the Netherlands were 16%, a much lower rate than the 80% in the USA.(4, 5) In the period before 1992 viral inactivation of clotting factor concentrates for HCV was inadequate. As a result almost 100% of the patients treated with large pool clotting factor concentrates in the Netherlands were infected with HCV. 80% of these patients now has a chronic HCV infection.(6)
Figure 1.1 shows the trend in life expectancy for Dutch patients according to a Dutch national survey from 2001 taking into account the effects of HIV and HCV.(7) The overall life expectancy of patients with haemophilia did not notably change between 1972 and 2001. Due to HIV and HCV infection life expectancy of patients with severe haemophilia decreased from 63 in the period between 1972 and 1985 to 59 years during the follow up between 1992 and 2001. For patients with moderate haemophilia, life expectancy increased from 65 to 67 years. However when HIV and HCV were excluded, life expectancy for the total population increased from 66 to 74 years, which is near normal.
Two other facts are indicative of the changes in quality of life of haemophilia patients. Between 1971 and 2001 the mean age of Dutch patients with severe haemophilia rose from 22 years to 32 years. And participation in the labour market increased even more. In 1971 the mean age of patients with severe haemophilia incapacitated for work without a job was 32 years, in 2001 this was 49 years.(8)

Figure 1.1. Life expectancy of Dutch patients

			1992-2001		
	1972-1985	**1985-1992**	**All patients (N = 967)**	**HIV negative (N = 511)**	**HIV and HCV negative (N = 967)**
All patients (years)	66	68	67	70	74
Dutch males	71	74	76	76	76
Severity of haemophilia (IU mL^{-1})					
Severe (< 0.01)	63	61	59	70	71
Moderate (0.01-0.05)	65	65	67	71	75
Mild (> 0.05-0.40)	-	74	73	73	75

Data from Plug et al.[7]

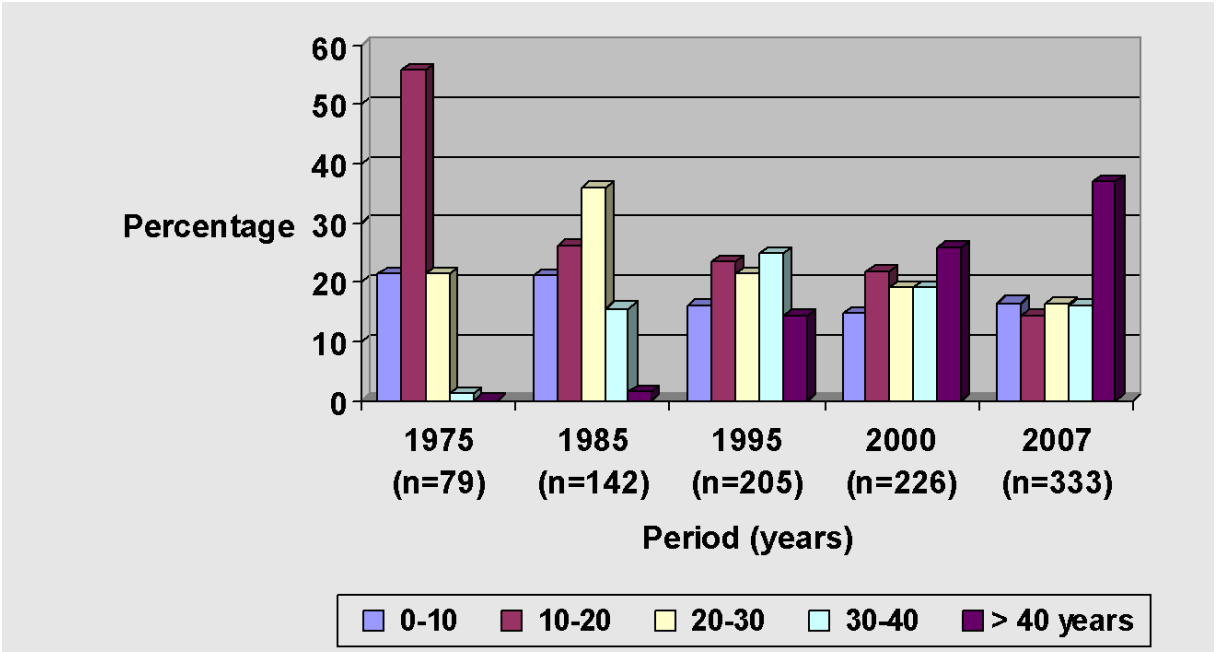
The Van Creveldkliniek cohort

The figures 1.2 - 1.4 depict the composition of the cohort of the Van Creveldkliniek department of haematology (VCK), UMC Utrecht, the major Dutch haemophilia centre. The data show that more than 300 men born before 1967 are treated at the VCK, and that the percentage of older men (> 40 years) with severe haemophilia is increasing.

Figure 1.2. Haemophilia population born before 01-01-1967 treated at the Van Creveldkliniek-Haematology between 01-01-2000 and 01-01-2007

	Severe (<1%)	**Moderate (1-5%)**	**Mild (> 5%)**	**Total**
Haemophilia A	132	35	104	271
Haemophilia B	12	4	15 (8)	31
Total	134	39	119	302

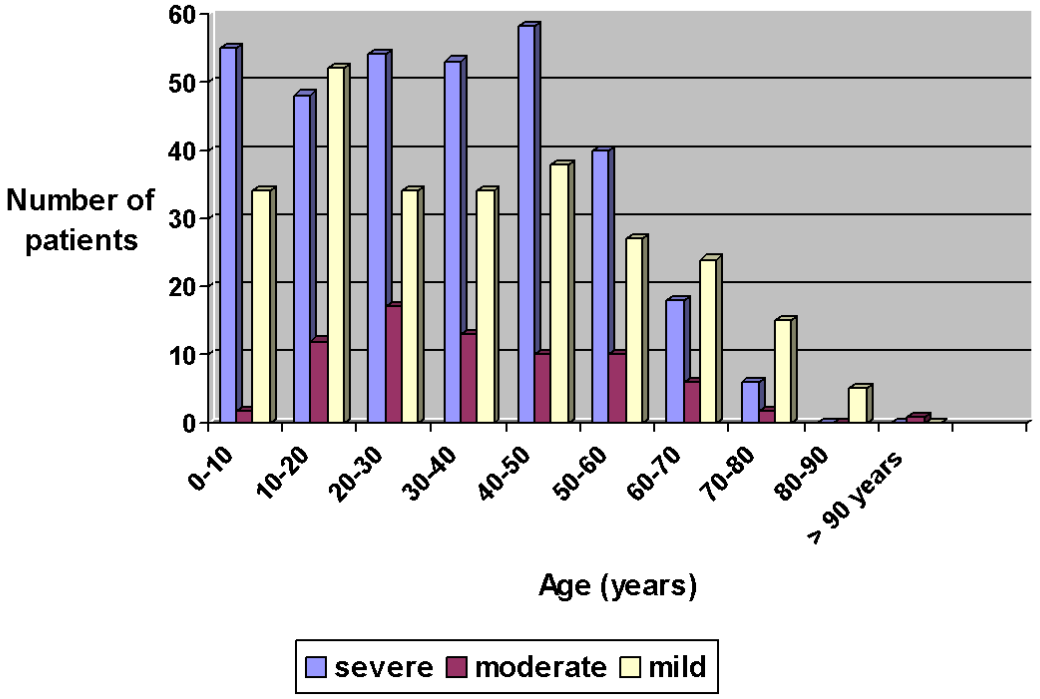
Figure 1.3. Percentage of patients with severe haemophilia treated in the Van Creveldkliniek-haematology according to period and age (years)



cijfers van grafiek toegevoegd voor Suzan Beijer

	1975 (N=79)	1985 (N=142)	1995 (N=205)	2000 (N=226)	2007 (N=333)
0-10	21,5	21	16,1	14,6	16,5
10-20	55,7	26	23,4	21,7	14,4
20-30	21,5	35,9	21,5	19	16,2
30-40	1,3	15,5	24,8	19	15,9
> 40 years	0	1,4	14,2	25,7	36,9

Figure 1.4. Number of patients according to age and severity of haemophilia treated at the Van Creveldkliniek-Haematology in 2007



cijfers van grafiek toegevoegd voor Suzan Beijer

age	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	> 90 years
severe	55	48	54	53	58	40	18	6	0	0
moderate	2	12	17	13	10	10	6	2	0	1
mild	34	52	34	34	38	27	24	15	5	0

In the period 2000-2007 the main cause of death in the cohort of haemophilia patients older than 40 years known at the VCK was malignancy (exclusive hepatocellular carcinoma). The data are shown in figure 1.5. Especially in mild haemophiliacs, who on average are older than the severely affected patients, malignancies will occur in percentages comparable to the general population. However, with increasing life expectancy the severe haemophiliacs will reach the same percentages. The data in figure 1.6, taken from a large national survey, show that the number of deaths because of HCV increased in comparison with the period between 1985 and 1992.(9) This is confirmed by the data from the VCK, in which 21% of deaths was related to hepatitis C.
In the total Dutch cohort studied by Plug *et al.* the number of deaths due to cardiovascular diseases has increased. This is not yet corroborated by the limited dataset from the VCK. With the increase in age of the VCK cohort it is likely that cardiovascular diseases will be diagnosed more frequently.

Figure 1.5. Cause of death and age at death between 01-01-2000 and 01-01-2007 of haemophilia patients born before 1967 known at the Van Creveldkliniek-Haematology

Causes of death	Severe	Moderate	Mild	Total (%)
HIV related	1			1 (4)

HCV related (carcinoma)	4 (2)	1 (1)		5 (3) (21)
Malignancy (exclusive hepatocellular ca)	3	1	5	9 (38)
Intracranial bleeding	3		1	4 (17)
Heart failure	1			1 (4)
Other	4			4 (17)
Total number of patients	**16**	**2**	**6**	**24**
Mean age (years)	56	72	74	62
Median age (years	57.5	-	74.5	63
Range (years)	38-73	71-73	68-79	38-79

Figure 1.6. Primary causes of death in a cohort of Dutch haemophilia patients

Cause of death	**1973-1986 N = 43 (%)**	**1986-1992 N = 45 (%)**	**1992-2001 N = 94 (%)**
AIDS	0 (0)	12 (27)	24 (26)
Hepatitis C	-	-	21 (22)
Hepatocellular carcinoma	-	-	5 (5)
Chronic liver disease	0 (0)	5 (11)	10 (11)
Malignancies	13 (30)	7 (15)	12 (15)
Haemorrhages	20 (47)	1 (2)	9 (10)
Cardiovascular disease?	4 (9)	10 (24)	16 (17)
Ischaemic heart disease	1 (2)	0 (0)	6 (6)
Cerebrovascular disease	3 (7)	9 (20)	4 (5)
Other causes or unnatural death	3 (5)	6 (9)	9 (10)
Sudden death, cause unknown	3 (7)	4 (9)	3 (3)

Data from Plug et al.[7]

Changing demographics

Demographic data on the population in the Western world indicate that we are entering a period in which the population will age rapidly. When Watson and Crick came up with their double helix structure of DNA in 1953, the average age of a European was 29.5 years. Today it is more than 38 years, and when the double helix will celebrate its 100th anniversary, the average age of Europeans is expected to be 49.5 years.(10) This trend illustrates human and medical achievements of an extraordinary character. In the first half of the twentieth century, we saw a steady improvement in housing facilities and hygienic measures. In the latter half, this was followed by strategies for the treatment of tuberculosis and the development of antibiotics. In the last decades all Europeans with a disease, be it chronic, genetic, rare or common, profited from the advances in medical science.

The aging issue is no longer limited to general society, but extends to the group of persons with haemophilia and other chronic diseases as well. Life expectancy of people with chronic diseases often used to be limited. Now they grow up reasonably fit and healthy and have

careers, build lasting relationships and start families. In the coming decades they will be seniors, who are expected to take care of the grandchildren. This increasing life expectancy leads to new challenges for both patients and their physicians and other health professionals: co-morbidities related to aging.

Chronically ill and co-morbidity in general

Co-morbidity is defined as the effect of all other diseases an individual patient might have other than the primary disease of interest.(11) There is currently no accepted way to quantify such co-morbidity.
With the advancing years people with chronic illness may develop one or more age-related diseases or disorders in addition to their primary illness. The age-related disease may adversely affect the chronic illness. Experiences of a large group of people with chronic illness were collected in a Dutch research project from the Dutch institute for health care research (NIVEL, Nederlands Instituut voor Onderzoek van de Gezondheidszorg), the Academic Medical Centre Amsterdam (AMC, Academisch Medisch Centrum Amsterdam, and the Institute for Public Health and Environmental Studies(RIVM, Rijksinstituut voor Volksgezondheid en Milieu).(12) This study shows that co-morbidity can lead to an increase in functional limitations, psychological complaints and symptoms, social and societal problems. Possible problems due to co-morbidity are shown in figure 1.7.

Figure 1.7. Problems that can be caused by co-morbidity

Functional limitations	*Social problems*
Physical detoriation, fatigue	Lack of understanding
	Reduction in social contacts
Psychological complaints/symptoms	*Societal problems*
Fear and depression	
Feeling of losing control	Reduced participation in labour and leisure activities
Lower capacity for self-care	Increase in health expenditure

On the whole these limitations may have a tremendous impact on quality of life. Generally people experience growing functional limitations and social problems as a serious loss of ‘quality of life’. Not just for themselves, but also for their partners, parents, friends, family members and colleagues. The burden for these ‘informal’ caregivers can be substantial when they are regularly confronted with a person who is facing loss of independence. Both patient and caregivers run a serious risk of stress and burn-out.

When focussing too much on medical and psychosocial problems associated with co-morbidity, the senior with a chronic illness is perceived as a person in a downward spiral, bereft, depressed and dependent, while one forgets to focus on the gains of getting older.(13) Aging may also have positive aspects for those who accept this last phase of life as an unexpected present. We have to realize that these seniors learned to overcome problems with the disease in their youth. Their experiences early in life with an untreatable, life-threatening disease may have given older haemophiliacs greater resilience than their healthy counterparts.

Living with Chronic Disease as a Strength

Living with a chronic illness teaches you things that you can apply to other illnesses and to the aging process.

Resilience helps to cope with changes that would be devastating at an earlier age. This has been learned through experiences of adversity.(13)

Co-morbidity and haemophilia

With increasing age haemophilia patients will suffer from age-related diseases too. Health care providers need to be aware of the aging issues in haemophilia. Then they will be able to respond to the needs and requests for help from patients, optimize haemophilia care and contribute to the quality of life of patients.
In general patients will first visit their general practitioner (GP) for medical problems which are not related to haemophilia. The GP can treat hypertension and diabetes mellitus in the same way as in other patients. When a haemophilia patient has to be referred to a specialist, this should preferably be a specialist in a hospital with a haemophilia centre.

Figure 1.8 shows the number of patients with severe haemophilia treated at the Van Creveldkliniek-Haematology (VCK) with co-morbidity complaints. All patients with severe haemophilia suffer from haemophilia arthropathy due to cartilage damage caused by repeated bleedings in the past.(14) This arthropathy can be quite disabling and painful and thus has consequences for social functioning.

Figure 1.8. Number of patients with severe haemophilia A and B known at the VCK (N =145) with co-morbidity in the period 2000 - 2007

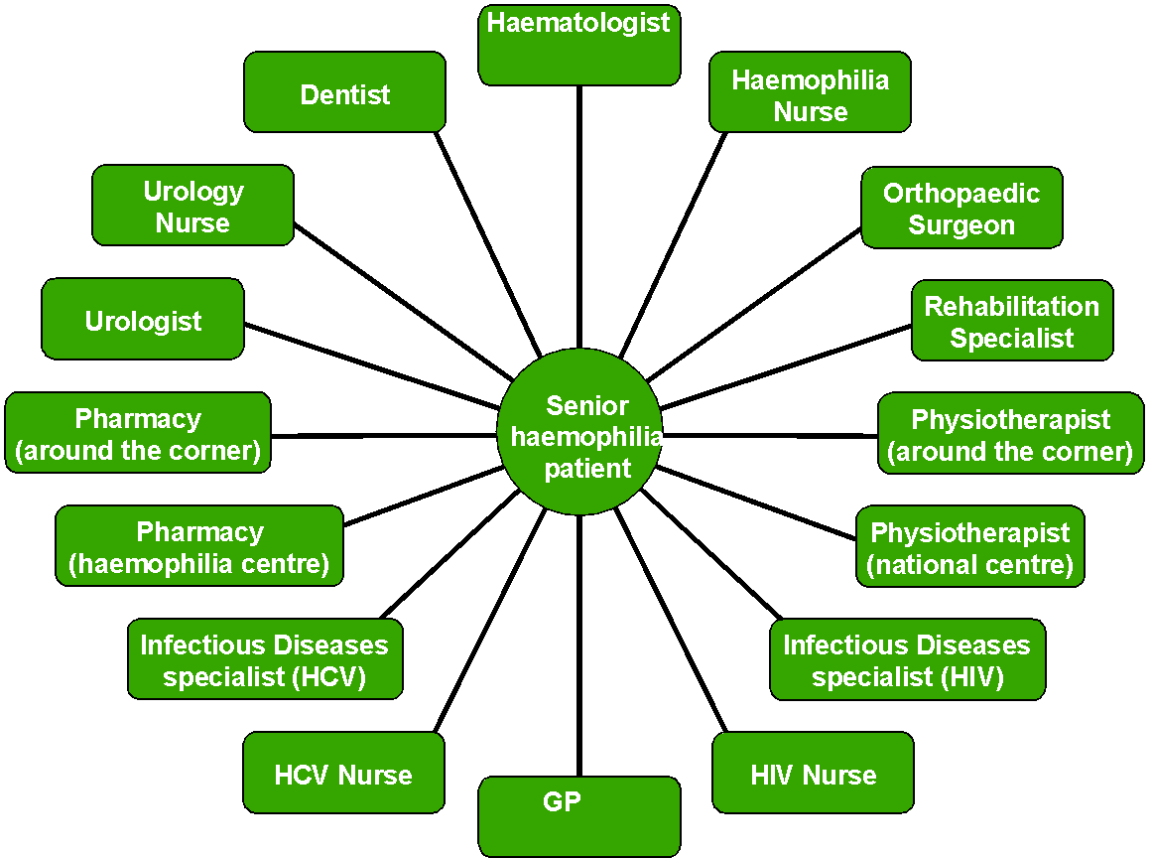
Severe arthropathy in 2 or more joints	145
HIV positive	17
HCV RNA positive	74
one or more other diseases	65

Patients with severe haemophilia are aware of their bleeding risk when they receive treatment for some ailment. However, clotting factor correction for the underlying disease is the easier part of treatment. Therefore patients should be treated in a comprehensive care centre. A multidisciplinary team should consist of an orthopaedic surgeon, a rehabilitation physician, a physical therapist, a social worker and a nurse, who all have to be familiar with haemophilia. In case of viral infections specialists on infectious diseases and a gastro-enterologist must be part of the care team.

Patients with mild haemophilia usually have little bleeding problems so they are not always aware that their haemophilia might interfere with treatment for other ailments. Sometimes they even forget to mention they have haemophilia. However, they will experience prolonged bleeding after surgery. Another risk factor for mild haemophilia A patients who have had little treatment in the past, is the development of inhibitors against factor VIII after infusion of clotting factor concentrates. This is an extra reason why careful follow up will be required.

It is obvious that co-morbidity in severe haemophilia is very common and requires extensive comprehensive care. Figure 1.9 shows the various specialists a senior haemophilia patient may have to deal with.

Figure 1.9. The senior haemophilia patient and the specialist around him



The complexity arises when other specialists are becoming involved. For them it is vital to understand the importance of contacting the haemophilia treater in order to guarantee adequate clotting factor correction during medical diagnostics, surgery and other medical interventions.

Although it used to be thought that haemophilia will protect against cardiac diseases, nowadays arterial sclerosis and cardiac diseases are seen more or less regularly. These diseases require proper therapy and open heart surgery may be necessary.(15) In these cases haemophilia treaters will not only advise on clotting factor correction but also on thrombosis prevention.

All in all, the haemophilia treater should be the key person in the co-ordination of care in order to guarantee the best level of care. Co-ordination by a haemophilia treater and education of patients and health care professionals may prevent complications.

Problems in senior haemophilia patients

Poor condition of joints and muscles
Stiffness, especially upon waking or after sitting for a long period of time
Limited walking, shopping
Fatigue due to viral infections
Limited ability to work / early retirement
Inability to carry out home treatment
The 'fear' factor (fear for lack of control)
Lack of co-ordination between specialists in case of co-morbidity

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Chapter 2. Coping with disability and co-morbidity: a patient's perspective

C. Smit

Changing perspectives

In 56 years of living with severe haemophilia I have experienced a number of remarkable transitions in haemophilia health care. The first transition was the one from no treatment at all for haemophilia to treatment becoming available. This marked the start of the best of times for haemophiliacs of my age: the period from the mid-sixties of the last century to the early eighties. My perspective changed from the prospect of a difficult life with a lot of pain to the expectancy of a near normal life.
The worst of times came in the early eighties, when it became clear that recipients of blood and blood products, and especially haemophiliacs, were among the first known high-risk groups for contracting HIV.(1) Later infection with the hepatitis C virus also was seen to have serious and even life-threatening consequences. When I found that I was indeed infected with HCV and HIV my life's horizon was shortened once more. The future brightened again as HAART-therapy for HIV became available and even more so when antiviral therapy led to the disappearance of my hepatitis C virus. Life expectancy was back to normal once more. And now I have actually reached that part of the human life-cycle where I really am of an advanced age.

Persons with haemophilia as well educated professionals

People with haemophilia, their partners and their families are mostly perceived as well-educated managers of their own disease. Nowadays in the Western world a child or a young adult grows up with the availability of modern blood clotting products. Patients or their parents can administer these products intravenously at home on an 'on-demand' basis or on a 'prophylactic' schedule. This development led to an enormous improvement in quality of life for haemophiliacs.
The main difference with the older haemophiliacs is, however, that the younger generation of haemophilia patients has little experience with spontaneous and rare bleedings. And that their haematologists and haemophilia-nurses also have no direct knowledge from the period that bleedings were quite common. The physicians from the early days of haemophilia treatment are growing older. Some of them have retired and some resigned because they blamed themselves for the viral transmission in their patients.
For the older haemophiliac this implicates that he is the well-educated professional who now has to deal with a new generation of caregivers largely unfamiliar with his medical and social past and the old 'typicalities of haemophilia'.

My own haemophilia career

Due to the lack of treatment for haemophilia I spent a lot of time in hospital during the first twenty years of my life. About ten of these twenty years I lived in a hospital bed. In spite of

this I never experienced that period in my life as a heavy burden. Contrary to general hospital policy in those days my friends were allowed to visit me. So like other youngsters, I played − whenever possible − with other children and enjoyed life at school.
It was much later in life that I realised the exceptional and rather personalized care I had received from my physician and especially from the matron of the hospital unit where I stayed most of the time. Like my parents, who always stimulated me to be as independent as possible, this matron was also concerned about my long periods of absence from school and friends. During my final high school year I even had permission to receive the whole class and teachers in the hospital to prepare for school examinations. And when other non-haemophilia patients complained about my apparent preferences, she told them that this was a necessary part of my medical treatment as well. Although she would never have put it that way, she perceived 'a patient as more than his illness'.

Needle phobia

From my early years in hospital I developed a strong aversion to the regular vena-punctures needed for the transfusion of clotting factor or − before that − fresh frozen plasma. Like many other haemophiliacs I developed 'needle-phobia'. At the age of fifteen I saw a psychologist to reduce this fear, however with little effect. It all disappeared the day that one of the physicians suggested that I should try to transfuse myself. It immediately went well and I have injected myself ever since. The phobia returns whenever I have to return for routine-checks and blood sampling. However, I now have a special card indicating that I may and can inject myself.
At the 2007 Global Nurse Symposium in Berlin a young adult with haemophilia from the UK told a similar story. The only difference was that his doctor suggested it when he was only three and a half years old!

A changing perspective

In the early seventies I left high school and went to university in another city. Quite soon I experienced that the approach to which I was used, was not that common. After two years of negative experiences I finally found a hospital that offered a more personal contact between hospital staff, the patients and their parents.
At that time the Dutch National Haemophilia Patient Society (NVHP) was founded and from the United States the concept of home-treatment was imported. I was among the first patients on home-treatment. The future looked bright. Half joking, half serious the haematologist told my mother that she could stop being concerned about my health. He did not expect me to need hospitalization for the next 25 years. Like all other men without haemophilia the biggest risk of hospitalization for me would be due to heart problems or other symptoms seen in hard-working career persons. And indeed, I did not need hospital admission for the next 30 years.
So in terms of 'quality of life' issues the perspective of haemophilia certainly has changed.

Co-morbidity

So this haematologist was right in his prediction. But what neither of us could have foreseen at the time were the consequences of viral infections. Morbidity and mortality for HIV and HCV became the dominant issue in the haemophilia population in the eighties and nineties. I have the fortune to be part of the one-third of HIV infected haemophiliacs with an infection survival of more than 25 years. It also was my fortune that the first manifestations of infection appeared when antiviral therapy had just been introduced. And by the time the complications

became more serious, HAART-therapy was available. I have needed hospital treatment for HIV twice. One episode was rather serious and had a tremendous impact on my life and that of my partner. While on holiday in France in 2001 I suffered acute renal failure due to one of the HIV inhibitors, Indinavir®. I became quite ill and needed about two weeks of intensive care at the hospital in Chalon-sur-Saône. Although I recovered rather well my general condition had deteriorated substantially. Due to the already existing bad condition of my knees, ankles and joints a knee-replacement seemed to be the next stop. However, thanks to intensive physiotherapy and functional gait training in the swimming pool this could be avoided. My wife advised me to buy a tailor made cycle [photo] and so I further improved my condition through intensive cycling. All in all the developments of the last twenty-five years have reduced the importance of haemophilia as a disease. For me the consequences of HIV infection have much greater significance. My greatest concern is the long-term effects of taking HIV inhibitors everyday and the progression of the infection.

Growing older

I entered into a long-lasting relationship rather later in life, so I was used to managing my own haemophilia. I deal with home-treatment without outside help. Fellow patients have told me that their wives assist them or even inject them. I now realize that self-treatment may become a problem for me in the future, but I will continue it for as long as possible.
Shopping is one of the things older haemophiliacs do not like because of their severe arthropathy. Our weekly shopping expedition generally takes over two hours of constant walking and standing. There have been periods that my condition did not allow me to accompany my partner, but at the moment that is not a problem.
Things become more complicated when one's partner falls ill. My wife once was unfortunate enough to break a leg. For three months I had to take care of shopping, housekeeping and daily meals. The mere fact that I have haemophilia did not entitle us to home help services. We managed without but it was very exhausting.

Because of my initial bad life expectancy, which did not improve in the period of the viral infections, I hardly gave matters like old age pension and financial future a thought. I never expected to reach retirement. When I was young my parents stressed the importance of good education in order to obtain a proper white-collar job. But once I entered university many things besides my study, e.g. the foundation of the Dutch Haemophilia Patients Society, kept me from my studies. I gradually became the eternal student. With the occurrence of HIV, the last thing I worried about was my pension.
Unlike many other people with HIV I continued and could continue working. So I accumulated a small pension. I had also received some financial compensation for HIV infected haemophilia patients through the Dutch government. With the money I bought my house. Since I have a partner, I feel a certain pressure to think about my pension. The only thing I have arranged is securing the house for my wife in case something happens to me.

Compliance

I absolutely comply with the necessary medical therapy for haemophilia and HIV. I am more than motivated to do physiotherapy and physical exercise (swimming and cycling). Thanks to these activities I have avoided a planned knee replacement. I also strictly abstain from using alcohol, tobacco or other drugs. More or less from the moment I knew of my own HIV and HCV risk I gave up alcohol.
The perfect patient! That remains to be seen. I have to admit that I absolutely do not comply with the rules on registering home-infusions and I definitely have a tendency to avoid my

dentist. I was also very reluctant to start antiviral therapy for HCV. So, I am not the ideal patient who always meekly follows every medical advice.

The quintessence of this long personal story is that in more than fifty years of life, I became a person with multiple chronic diseases and with a broad range of health care contacts. It's my belief that although this is my own personal story, it is comparable with the experiences of many other people with chronic disease and co-morbidity. Details may be different, but the general picture will remain the same.

Three problems with co-morbidity

Three problems worry me specifically. The first problem is the lack of co-ordination between medical specialists, the second is polypharmacy − the use of multiple medications − and as a consequence of these first two problems a third problem occurs which I prefer to address as the 'fear' factor.
About polypharmacy, all in all I probably do not take that many different medications. But I already have experienced quite a few problems with the so far unexplainable complications occurring due to the interference of my HIV medication and haemophilia, predominantly bleeding complications. My acute renal failure was due to one of the HIV inhibitors.
Enter a third medical discipline not familiar with these two diseases and a disaster is waiting to happen. In such situations I − as a patient − have experienced a lack of co-ordination, willingness and time to discuss things before acting. Some specialists primarily act on what they perceive as the medical problem. After a number of these experiences as a patient I automatically developed the 'fear' factor.

The 'fear' factor

Like other persons with severe haemophilia I have a special type of 'fear'. The 'fear' of a lack of co-ordination, a lack of control when you are hospitalized, when you need medical treatment from physicians who have no experience with haemophilia or when you are involved in a serious traffic accident.
In all these cases you, who are a well-educated manager of your own disease, may not be able to influence or check the treatment you receive. The ambulance may take you to a hospital that has a bed available but no experience with haemophilia, and then valuable time may be lost.
Part of the 'fear' of older people with haemophilia is that they are often not in good physical shape due to orthopaedic or viral complications. So when, for instance, minor or major surgery is proposed we not only fear the operation, but the consequences of this operation for total body functioning. To us our state of health is a delicate balance. 'Vulnerable' actually may be a better term.
In the final chapter of this book practical advice how to deal with fear is given.

Improving health care settings for people with co-morbidity

In recognition of the expected growth of the number of people with haemophilia and co-morbidity and the problems that already exist, a way to adjust the health care system to the needs and wishes of patients, especially older patients, should be found. In a study NIVEL, RIVM and AMC discussed the co-ordination issue with several medical experts. They all held different opinions. At the end of the day no consensus for a solution had been reached.(2)

In the last couple of years I have regularly discussed the issue of co-morbidity and its co-ordination of care problems. One thing I have learned is that geriatric patients have problems which are similar to those perceived by people with co-morbidity; i.e. growing functional limitations, psychological symptoms and social and societal problems.
In rehabilitation, paediatric and geriatric care a holistic approach has been developed in which the patient is seen as a person in relation to his environment. Care encompasses not just the child but parents and family as well. This definitely compares with the way I grew up in the hospital setting where the matron regarded her patients as more than their illness. Although for haemophilia this concept already exists since the introduction of specialised comprehensive care centres, I wonder whether it is also possible to introduce a comparable hospital setting for patients with other multiple chronic diseases. This will be in sharp contrast with the way most hospitals are now organized, but it is worth the effort to start a number of experiments.
Of course, the approach cannot be too generalised. Co-morbidity problems are often so complex that highly specialized knowledge is absolutely necessary. A special clinical and outpatient facility for people with co-morbidity problems could be introduced.

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How to avoid complications?

Practical advice for haemophilia patients with co-morbidity and their care givers

Some advice can be given to haemophilia patients with multiple chronic diseases and their partners that may suffice to avoid some – maybe not all – complications. Useful suggestions from patient organisations or a nurse practitioner could be:

1 Besides the haemophilia patient society, to become a member of one or more patient organisations dealing with your most important diseases, to read their information materials and to surf along the internet.

2 It is advisable to stay in regular – at least once or twice a year – contact with medical or nursing staff of your haemophilia centre. Although there may be no acute medical reason, it is useful to know them and to be up to date about practicalities like changes in emergency telephone numbers. This may be also true for co-morbid diseases.

3 Always inform any physician or paramedical person you have to see about a medical problem not directly related to your haemophilia. Inform them that your haemophilia treater should always be contacted to discuss the treatment regimen. And for your own safety, personally call your specialist and check if everything is co-ordinated.

4 In case of emergency hospitalisations or traffic accidents, always instruct your partner or family members that they should inform your haemophilia treater when you are hospitalised in another hospital. For these situations it is also sensible to wear a Medic Alert bracelet or pendant with your medical data and an up-to-date telephone number that can be contacted in case of emergencies. Also add the telephone number of your haemophilia centre in your mobile phone.
Carrying an USB-stick - Medstick® - with your medical data is a modern sophisticated way to have all information with you. Your medical data can be available in different languages (Dutch, German, English, French)(www.cinsol.nl)

5 When you are admitted in another department than the one you're familiar with, be aware that the hierarchy of the hospital system may cause co-ordination problems. In most hospitals the doctor responsible for your daily care is a physician working in that particular department who may not be very familiar with your haemophilia and other diseases. Also the nurses or allied health staff usually are not well-informed about the daily treatment aspects of your other diseases. They may be surprised that you prefer to do parts of the treatment, for example intra venous injections, yourself and do not know that you are expert in performing it.
It is advisable to discuss this as soon as possible after admission and inform the physician in charge or the ward-nurse that you are used to do part of the medical care yourself. Also if you are afraid of certain situations tell them in advance about your possible fears and worries.

6 It is always wise to determine in advance what you need to organise in order to receive adequate medical care. It is also advisable to tell your partner, friends or family members what you want them to do in case of an emergency. You may want to write down a short memo of these instructions as well.

Chapter 3. Haemophilic arthropathy: Rehabilitation and orthopaedic surgery

L. Heijnen & P. de Kleijn

Rehabilitation: the patient directs his activities

Introduction

Severe haemophilia patients born before 1950, well before the introduction of replacement therapy, generally have 4-6 arthropatic joints.(1) These joints have a limited range of motion and are more or less painful and/or stiff. Patients all experience limitations in their activities of daily life (ADL) and various restrictions in participation in society. Treatment may be difficult as the patient has to realize he has joint problems and be willing to accept help. A full treatment plan with intermediate and ultimate goals has to be drawn up based on the problems identified by the patient. And when physical therapy is initiated, it is essential that the patient has confidence in the physical therapist.
If pain is a major issue, this has to be addressed first; treatment modalities are pain medication, distal traction, TENS (Transcutaneous Electrical Nerve Stimulation) and hot packs.

Pain medication in the Van Creveldkliniek-Haematology:
1. Paracetamol is the initial medication of choice; if not effective
2. Paracetamol and codeine (10-20 mg max 6 times a day)
3. For severe pain paracetamol and a muscle relaxant
4. For very severe pain morphine (MS Contin®)

Treatment includes remedial exercise (= joints and muscles) and functional training: hydrotherapy, walking (with or without an aid), climbing stairs and cycling. Functional training helps to minimize periods of limited activity, and enables the patient to resume ADL, social participation and work.

This chapter contains the descriptions and comments of two case studies. The first case describes a haemophilia patient with severe arthropathy who had conservative treatment. The second case is a patient who underwent multiple orthopaedic procedures for severe arthropathy.

Case 1, conservative therapy

Patient 1, 72 years of age, severe haemophilia A, and a ‘life-long’ inhibitor. He has equinus feet due to calf bleeds and severe arthropathy in ankles, knees and elbows; he also has recurrent wrist bleeds and in recent years right shoulder bleeds.
Due to his inhibitor he did not benefit from replacement therapy when this became available. He wished to stay active for as long as possible, took up swimming two times a week in the 1970's and added a daily yoga routine in the 1980’s. This enabled him to hold down a fulltime

job. Until the age of 69 he was the managing director of a training institute for hostesses; a job that required a great deal of standing and walking everyday.
He drives a car; the limited range of motion of his legs prevents him from riding a bicycle. He noticed a deterioration in mobility when getting older. So he determinedly continued his daily 1½ hours walks in spite of the serious pain. He only takes an occasional paracetamol because with adequate painkilling he tends to be too active thus causing bleeding in joints or muscles.
He is aware of a heightened risk of falling due to the limited range of motion in his arms and legs. He trains for special skills in both balance and controlled falling. With this strategy he maintains a relatively relaxed gait and he hardly ever falls.
He is an avid bird watcher and coordinator of a bird ringing group; therefore he has to be able to handle uneven terrain. He wears orthopaedic shoes for equinus feet and has one pair manufactured especially for bird watching. To take the strain of his limbs during walking he very recently started using a walking-bicycle. [photo]

Comments

This patient made the most of his physical capacities by prescribing himself intensive daily exercises and physical activities. Only twice did he need help from a professional physiotherapist. The first time was after a prolonged hospital stay, when he was immobile and needed help with ADL activities. He regained his former mobility only after an intensive clinical exercise programme. The second time he had three bleeds in his right shoulder and needed the help of a local physiotherapist to regain function. In this period he had to give up swimming because of problems getting in and out of the swimming pool.

Case 2, surgical intervention

Patient 2, severe haemophilia A, 64 years of age. Due to a major forearm bleeding at 4 years of age he developed a Volkmann contracture, with his forearm in fixed pronation and his wrist and fingers flexed. He was hospitalized for 11 months and it took 3 years of physiotherapy to regain maximum extension of the elbow. Numerous bleeding episodes in both ankle and knee joints resulted in a painful arthropathy at first mainly in the ankle joints.
A multi-joint procedure was indicated in the late 1990's. He underwent bilateral ankle arthrodesis, and bilateral total knee replacements one week later. The rehabilitation programme was started on day 2 after the total knee replacements. And this programme finished about one year later.
He reports his life has changed dramatically since he had surgery.

Social situation before surgery

Patient 2 started his career as a technical draughtsman, a job that kept him on his feet for eight hours a day! He drove a manual transmission car (by choice). He began reading politics at the Erasmus University Rotterdam after he was made redundant on medical grounds. After finishing this study, he worked for many years as a policymaker for the Department of Social Affairs.

Pain

Over 20 years ago patient 2 was advised by his haemophilia consultant to have bilateral ankle arthrodeses. He refused and he started using pain medication: first paracetamol, which had no effect, and then pethidine. Due to side effects like drowsiness, he discontinued this pain medication.
After work, meeting in the pub with his colleagues, he usually had three beers in quick succession, so pain would not interfere with him enjoying a chat with his mates. At a later stage he was told to give up alcohol because of his hepatitis C, so he mentally raised his pain threshold. During those years he became less and less active, could barely walk a mile and feared the pain he would get the next day after performing (extra) activities. The main reason he did not want surgery for many years was because he was told that 'the first days after surgery are hell because of the amount of pain'. In the late 1990's he met a fellow haemophilia patient, who had had a total knee replacement and who reassured him the post-operative pain was bearable.

Post-operative rehabilitation programme

Knee flexion and extension training was assisted by a physiotherapist. Often knee flexion is difficult to train and optimal flexion is not guaranteed, not even the same range of motion as preoperatively. Therefore a Continuous Passive Motion (CPM) machine was used clinically, and also after discharge for some weeks in a Rehabilitation Centre. Two weeks after the total knee replacement, when the operation wounds were sufficiently healed, he exercised in the pool on a daily basis, at first in a special part with barriers. This is the only way to do functional exercise for the knees, with no weight bearing on the ankle joints. The buoyancy of water guarantees a reduction in weight, but a pair of splints is necessary as well. [photo] After three months weight bearing is slowly increased till full weight bearing. Only then walking distances, work and leisure related activities can be trained in a functional way.

Comments

Patient 2 indicates to have a totally different life after surgery; he wanted to profit from surgery during his retirement years, and succeeded. He reports he has walked 15 km on the beach, with a backpack. He has used the stairs to go to the 11th floor and needed to rest only once. He can handle rough terrain, slopes and city traffic, but mainly he feels 'free' because he does not have to balance his activities for fear of the pain next day. Unfortunately he is not able to flex his knees the way he could before surgery. Preoperatively he did not ride a bike because of the pain, and now he is not able to ride a bike because of restricted knee flexion. It took him a year to accept this situation. Shorter distances he does on foot and longer distances by car. He enjoys fitness training once a week and in winter hydrotherapy with fellow haemophilia patients once a week as well. He does not regret the decision to go for the multi-joint procedure.

Balance dysfunctions and risk of falls

Patient 1 trains for balance and falling skills. The literature shows that he is a prudent man. Between 30 and 40% of community-dwelling adults over the age of 65 fall each year. Falls are associated with increased morbidity, mortality and referral to nursing homes. Risk factors for falls include muscle weakness, a history of falls, use of four or more prescription medications, use of a walking aid, arthritis, depression, age older than 80 years and impairments in gait, balance, cognition, vision and activities of daily living.(2)

Tripping is the most frequent cause of falls. Patients with osteoarthritis of the knees had a 37% lower obstacle avoidance success rate, a 54% lower single-leg stand duration, and a 24% greater Body Mass Index compared to healthy age-matched control subjects.(3)
This is also the case for patients who had bilateral total knee arthroplasty.(4) In a group of 6641 men and women aged 75 years or older 35.2% has knee pain and 6.8% knee osteoarthritis (OA). 3992 patients sustained a fall and a total of 436 non-vertebral fractures were reported. Increasing severity of knee pain was associated with a greater risk of falls and hip fracture. The clinical diagnosis of knee OA was also associated with an increased risk of fractures. The most effective fall prevention strategies are multi-factorial interventions targeting identified risk factors, exercises for muscle strengthening combined with balance training, and withdrawal of psychotropic medication. Home hazard assessment and modification by a health professional is also helpful.(2)

The role of osteoporosis

A relationship between haemophilia and osteoporosis has been suggested. Wallny *et al.* studied 62 male patients with severe haemophilia with a mean age of 41 years. Reduced bone mineral density (BMD) defined as osteopenia was found in 43.5% and osteoporosis in 25.8%. (5) An increased number of joints with haemophilic arthropathy and/or increased joint damage were associated with a lower BMD in the neck of the femur. Pronounced muscle atrophy and loss of joint movement were also associated with a low BMD. Further more hepatitis C, low mean Body Mass Index, and age were found to be additional risk factors for reduced BMD. The main cause for reduced bone mass is most probably haemophilic arthropathy with chronic pain and loss of joint function leading to inactivity.

Conclusion

Joint replacement therapy can improve activities, participation and quality of life of elderly patients with painful arthropathic joints. For a good result the patient has to put time and effort in a post-operative rehabilitation programme. If replacement therapy is not available or inhibitors prevent surgery some very motivated patients manage to live admirably active lives due to individually tailored daily exercise programmes. In general, physical activity is especially important for the elderly (haemophilia) patient as it can significantly reduce the risk of cardiovascular disease, diabetes, some forms of cancer, osteoporosis, obesity, falls and fractures and some mental health problems.(6)
So far there is no literature on the problem of falling in people with haemophilia. Street *et al.* have commenced a study to evaluate the magnitude of problems of balance dysfunction and falls in people with haemophilia (aged > 30 years), and to determine the feasibility of a home exercise programme targeting balance training for this group.(7)

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Chapter 4. HIV in haemophilia: natural history and complications of treatment

M.E. van der Ende

Introduction

Between 1978 and 1986 haemophilia patients treated with plasma derived clotting factor concentrates were exposed to human immunodeficiency virus (HIV-1). World wide many patients have died of AIDS related diseases and opportunistic infections between 1985 and 1996. The introduction of highly active antiretroviral therapy (HAART) in 1996 resulted in a dramatic decline of HIV related morbidity and mortality.(1) For many haemophilia patients HAART either came too late, or its effect was hampered by a poor baseline immunological and virological status which limited immune recovery. Approximately 35% of the infected patients has survived and is well 20-25 years after infection. Several cohort studies and national registries give detailed information on haemophilia cohorts, showing survival trends and causes of death (table 4.1). These studies are important in understanding the natural history of HIV and the impact of HAART in individuals with haemophilia. In this chapter a brief overview of the markers of HIV-1 disease progression in individuals with haemophilia will be given. Hepatotoxicity of antiretroviral drugs in HIV/Hepatitis C (HCV) co-infected haemophiliac patients and increased bleeding tendency will also be discussed.

Figure 4.1. Progression to AIDS and mortality in cohorts of HIV infected haemophiliacs

Reference	Patients N	Median age at infection	Median follow up time and study period	Death N (%)	AIDS N (%)
5 Roosendaal	52	19 (5-62)	14 yrs 1981-1995	21 (40%)	23 (44%)
4 Rosenberg	999	63% < 25 yrs	7.5 yrs 1982-1992	265 (27%)	283 (28%)
6 Lorenzo	94	17.3 (1.1-65.5)	16 yrs 1982-1998	42 (45%)	31 (33%)
7 Darby	1246	25% <15 yrs 49% 15-35 yrs	1985-2000	802 (64%)	610 (49%)
8 Sabin	111	22 (2-77)	14.3 (0.8-25) yrs 1979-2004	74 (67%)	59 (53%)
11 del Amo	585	44% < 15 yrs 45%: 15-35 yrs	1985-2003	354 (60,5%)	208 (36%)
12 Arnold	660	18 (1-64)	21 yrs 1982-2003	406 (61.5%)	283 (43%)

Disease progression in HIV positive haemophiliacs with long-term follow up

The rate of HIV infection among haemophiliacs in the United States is estimated at 80%.(2) The peak of infection is to be found in 1982-1983. Infection rates declined rapidly in 1984-1985, and fell to zero after 1986. In the Netherlands only 16% of patients with

haemophilia was infected with HIV.(3) The onset and peak of infection occurred one year later than in the USA. A Multicenter Hemophilia Cohort Study (MHCS) from the USA showed the cumulative incidence of AIDS and death in 999 HIV positive patients through 31 December 1992.(4) Patients were stratified in three birth cohorts: born before 1943, born between 1943-1957, and born in 1958 or later. Individuals in these groups were 35+, 20-34 and 0-19 years old at the onset of the HIV epidemic in January 1978. Progression to AIDS was most rapid in the oldest age group. Median time-to-AIDS was 9, 13 and >14 years in the three groups respectively. The correlation of younger age at seroconversion and improved survival was observed in other studies.(5, 6, 7, 8) Younger age at seroconversion appeared to be one of the most important factors associated with improved survival before the introduction of HAART. Such an age gradient would be anticipated from the greater number of thymic cells in younger individuals, increasing the chance of ongoing replenishment of the CD4 T-cell population.(9) In a meta-analysis of 38 HIV cohort studies, the effect of age at infection on disease progression was noted to be more pronounced among individuals with haemophilia.(10)
After the introduction of HAART mortality from HIV related causes fell dramatically in all age groups. Differences among age groups were no longer statistically significant.(7) However, from 1997 onward the reduction in AIDS related deaths has been accompanied by an increase in the number of persons at risk for death from liver related conditions. An increase in liver related deaths has been observed in several cohorts. The percentage has risen from 7% before 1996 to 25% in 1997-2000 and reached 78% in 2001-2003.(7, 8, 11, 12, 13) Liver disease is now the most important cause of death in all patients with haemophilia and HCV, not just those who are HIV positive.(13) HCV induced liver disease has been shown to progress more rapidly in HIV infected individuals (14), even when on effective antiretroviral therapy. Surviving pre-HAART HIV positive haemophiliacs will exhibit end-stage liver disease earlier than HIV negative patients with haemophilia and HCV.(15)

Side effects of HAART in haemophiliacs

HAART can suppress virus replication to the level that the virus is unable to generate drug resistance mutations. Theoretically HAART should work indefinitely, but may be impeded by long-term side effects. Most HAART regimens consist of nucleoside analogues (NRTIs) combined with a non-nucleoside analogue (NNRTI) or a protease inhibitor (PI). Long term side effects currently studied are metabolic complications, such as diabetes mellitus, hyperlipidaemia, lipodystrophy, abnormal fat distribution and osteopenia. Hepatoxicity is another side effect of HAART. All NRTIs can cause lactic acidosis and severe hepatomegaly with steatosis. Nevirapine, a NNRTI, is associated with an increased risk of drug associated hepatitis (1-2%), especially in patients with higher CD4 cell counts.(16)
Because of the underlying liver disease, HIV/HCV positive patients are more prone to severe side effects of antiretroviral drugs. Some, but not all, studies suggest that drug induced hepatotoxicity may be more common in persons with HIV-HCV co-infection, particularly those taking protease inhibitors.(17) However, 88% of a large HIV-HCV co-infected cohort did not experience substantial hepatotoxicity, indicating that with close monitoring HAART can be safely administered to most patients.(18)

Case: Liver intoxication due to neviparine

A 42-year old Caucasian male with severe haemophilia A had an active hepatitis C which failed to respond to treatment with alpha interferon in 2003. Treatment of his HIV infection was started with tenofovir, lamivudine and nevirapine. His ALAT and ASAT were elevated, 2 to 3 times the normal range. After four weeks liver functions were stable. Six weeks after initiating HAART ALAT and ASAT increased to 1314 and 691 U/l respectively. He developed ascites and became jaundiced. Bilirubine peaked to 345 U/l. Plasma HCV RNA was stable, 5.5 x 10^5. Nevirapine was discontinued and replaced by lopinavir. He slowly recovered and is relatively well now.

Increased bleeding tendency due to HIV protease inhibitors has been reported in 15% of patients.(19, 20, 21, 22) No haemostatic cause for the increased bleeding tendency has been identified. Bleedings may be unusual because of their atypical location in soft tissues or muscles, or bleeding frequency may be higher than usual.
To prevent and treat co-morbidity, treatment of HIV positive haemophilia patients warrants good co-ordination between the infectiologist or AIDS specialist and the haemophilia specialist. In case of increased bleeding tendency adequate prophylaxis with clotting factor concentrates is indicated to prevent bleedings. In some cases these bleedings require discontinuation of the protease inhibitor. Patients should be informed about this potential risk and closely monitored. In case of HCV co-infection with progressive liver disease a gastro-enterologist must be consulted.
As HIV infected haemophiliacs often visit many different specialists (see also Chapter 1, figure 7) good co-ordination of care has to be ensured. Frequently it is the haemophilia specialist who takes the part of co-ordinator in order to optimize and maintain good quality of care. Definitely the haemophilia specialist has to be informed whenever patients are admitted to the hospital for complications of HIV. The infectiologist should realize that for many ‘harmless’ medical diagnostics, for example arterial puncture or bronchoscopy, clotting factor correction is indicated.

In conclusion

Persons with haemophilia born before 1985 are often infected with viruses transmitted by plasma products. They have survived these infections for over two decades. They are HIV/AIDS survivors, three-fifths of them are on HAART, and half of them no longer have

detectable HIV-1 in their plasma. Prospective follow up will be needed to see whether long-term complications from HIV and/or HAART and HCV will emerge.

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Chapter 5. Hepatitis C in haemophilia: natural history and treatment

E.P. Mauser-Bunschoten, D. Posthouwer & R.J. de Knegt

Introduction

Nowadays hepatitis C is a major co-morbidity in patients with inherited bleeding disorders and a leading cause of morbidity and mortality in patients with haemophilia.(1,2)
Since the 1960s haemophilia patients have received intravenous factor VIII and IX replacement therapy prepared from plasma. However in the 1970s it appeared that patients treated with plasma products developed jaundice with biochemical evidence of hepatitis.(3) In the absence of detectable hepatitis A and B virus the disease was called non-A non-B hepatitis.(4,5) After identification of the hepatitis C virus (HCV) in 1989 it was found that this virus was responsible for the majority of non-A non-B hepatitis in patients with haemophilia.(6) 98% of haemophilia patients treated with large pool products were infected with HCV against 66% of patients treated with cryoprecipitate.(7) In the early 1990s methods were developed to adequately inactivate HCV and subsequently donor screening for HCV was introduced resulting in HCV safe products.(7,8,9)
Once infected, about 10-20% of patients are able to clear the virus spontaneously, while the others develop chronic hepatitis C infection. Untreated HCV infection induces liver fibrosis progressing to cirrhosis. Patients with cirrhosis may develop decompensated liver disease and/or hepatocellular carcinoma.
As approximately 20% of chronically infected patients will develop End Stage Liver Disease (ESLD) after 20 years of infection, antiviral therapy is warranted in order to eradicate the hepatitis C virus and thus prevent the development of severe complicated liver disease.

Progression of HCV in patients with inherited bleeding disorders (10)

In an international multi-centre cohort study co-ordinated by D. Posthouwer the progression to end stage liver disease in patients with inherited bleeding disorders and hepatitis C was investigated.(10) In this study of 847 haemophilia patients with chronic hepatitis C the risk of development of ESLD was assessed. Patients had been infected between 1961 and 1990, and were followed up to August 2005. Patients suffered predominantly from haemophilia A and B (91%). The data of this group are shown in figure 4.1.

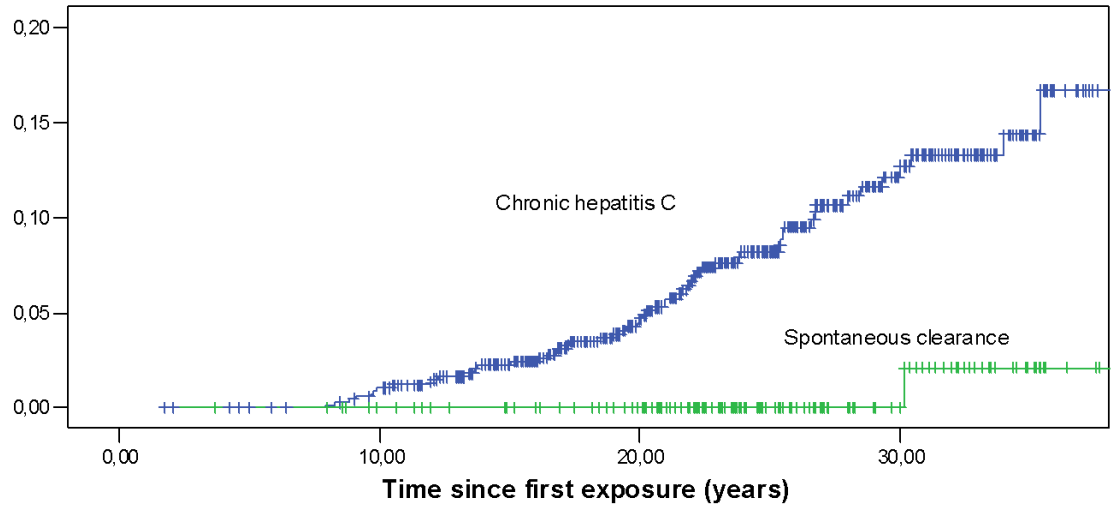
Figure 4.1. Patients (N = 847) with inherited bleeding disorders and hepatitis C

	years	years range
median age at infection	14	< 1 –77
median age at end of follow-up	43	11 –87
median follow-up time since infection	27	3-42
total follow-up time since infection	22,259	

Of 847 patients, 160 (19%) spontaneously cleared hepatitis C virus and 687 (81%) developed chronic hepatitis C. Co-infection with HIV was present in 210 patients (25%).

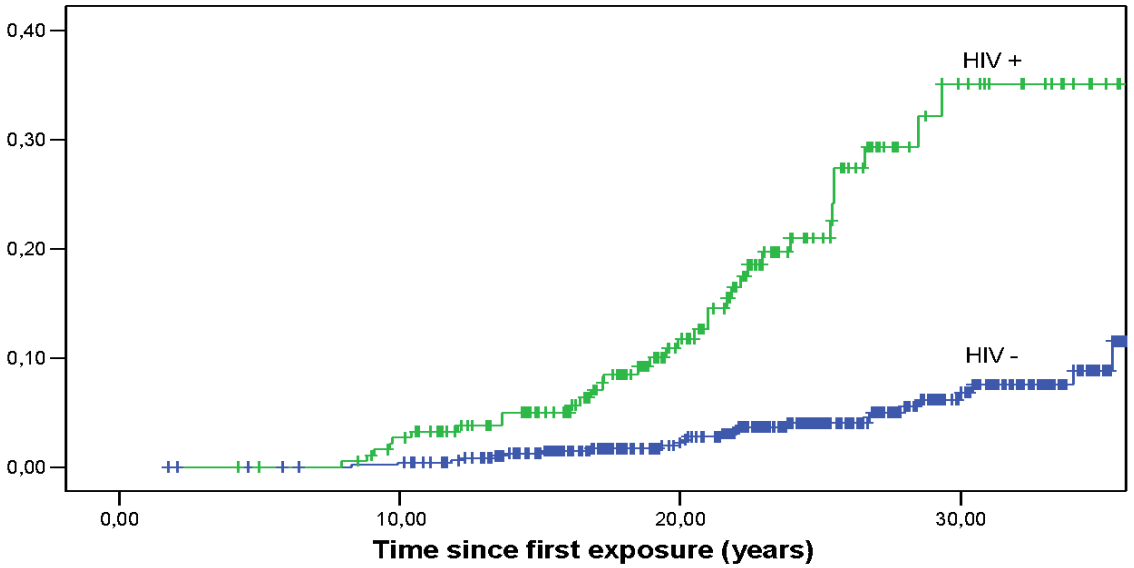
After 35 years of infection the cumulative incidence of End Stage Liver Disease in all patients with chronic hepatitis C was 17.1% (70 patients). In contrast End Stage Liver Disease developed in only 2.1% of patients who spontaneous cleared HCV (p<0.001, Figure 4.2). In this group only one patient with alcohol abuse developed End Stage Liver Disease.

Figure 4.2. Cumulative incidences of End Stage Liver Disease in patients with chronic hepatitis C (N = 687) and patients who spontaneously cleared HCV (N = 160)



HIV was an important determinant of outcome; the cumulative incidence of End Stage Liver Disease increased from 11.5% in HIV negative patients, to 35.1% in HIV co-infected patients (p<0.001, Figure 4.3).

Figure 4.3. Cumulative incidences of End Stage Liver Disease in patients with chronic hepatitis C according to their HIV status (190 HIV+, 497 HIV-)



After 20 years of infection, the incidence rate of End Stage Liver Disease for HIV negative patients with chronic hepatitis C was 0.53 per 100 person years, compared to 2.63 for HIV co-infected patients. Independent risk factors of End Stage Liver Disease were:

- HIV co-infection (hazard ratio 13.8),
- mature age at infection (hazards ratio 2.3 per 10 years),
- alcohol abuse (hazards ratio 4.9), and
- presence of genotype 1 (hazards ratio 2.2).

Figure 4.4 shows the characteristics of the development of End Stage Liver Disease (ESLD). Overall, 199 patients (24%) died. 73 patients (37%) died of HIV/AIDS, 55 (28%) of liver disease, and 71 (36%) due to other causes.

Figure 4.4. Patients with chronic hepatitis C developing ESLD

Patients with chronic hepatitis C developing ESLD:	70
not treated with antiviral therapy	58
after unsuccessful antiviral therapy	12
Time between infection and ESLD	median 21 years
	range 8-36 years
Patients with 2 or more features of ESLD	50
Patients with liver failure	59
Patients with hepatocellular carcinoma	13
Patients with liver-related death	55
Patients with liver transplantation due to ESLD	9

Therapy for Hepatitis C

In the late 1980s interferon-α (IFN) monotherapy became available resulting in eradication of hepatitis C virus (HCV) in 10 to 30% of patients with haemophilia.(11,12) The addition of ribavirin to IFN resulted in significantly higher sustained response rates of 30-50%.(13,14)

Currently the state-of-the-art treatment for HCV consists of pegylated interferon (PegIFN) once a week and ribavirin 800-1200 mg daily.(15,16)
Duration of treatment varies with HCV genotype. In patients with genotype 1 and 4 without significant fibrosis of the liver, defined as stage F0 or F1 according to the Metavir classification, therapy may be postponed. Patients with genotype 1 and 4 with significant fibrosis or cirrhosis (i.e. F2, F3 or F4), are treated for 48 weeks. However if HCV load has decreased less than 100 fold after 12 weeks of treatment, or HCV is still detectable after 24 weeks, treatment is discontinued. Patients with genotype 2 and 3 are treated for 24 weeks irrespective of the amount of liver damage and effect of therapy. In this group HCV-RNA is not measured during therapy. Effectiveness of therapy i.e. sustained virological response (SVR) is evaluated four weeks after end of therapy by HCV-RNA measurement.
This treatment schedule yields response rates of 40-50% in haemophilic patients with HCV genotype 1 and 4 and 80-90% in genotype 2 and 3. These results are the same as in non-haemophiliacs. This implicates that around 50% of patients are treated without success and at risk for developing end stage liver disease. Figure 4.5 shows the responses to IFN-based therapy.

Figure 4.5. Response to IFN-based therapy: overview of the selected studies in patients with haemophilia infected with HCV (N = 35) (Posthouwer, 17)

Treatment regimen		**Nr of studies**	**Nr of patients**	**Median SVR[1] (range)**
HIV negative				
IFN mono	Naïve patients	12	269	20% (0-50%)
IFN and riba·				
	Naïve patients·	7	295	39% (29-57%)
	Non-responders[2]	2	72	35% (33-36%)
	Mixed naïve patients and non-responders	2	72	35% (27-41%)
PegIFN and riba·	Naïve patients	2	168	57% (55-59%)
Mixed HIV negative and HIV positive				
IFN mono·	Naïve patients	7	152	25% (0-50%)
IFN and riba·	Mixed naïve patients and non-responders	1	28	71%
HIV positive				
IFN mono·	Naïve patients	1	7	0%
IFN and riba·	Naïve patients	1	20	40%

1) SVR – sustained viral response
2) Non-responders include relapsers and non-responders to previous antiviral therapy

Side effects of hepatitis C therapy

Side effects of treatment with interferon and ribavirin are common. Flu like symptoms and weight loss in excess of 5 kg are seen in over 60% of patients. Psychological problems like irritability and concentration problems occur in more than 80% of patients and severe

depression requiring antidepressant drugs in one fifth of patients. Weight loss and haematological abnormalities (anaemia, neutropenia or thrombocytopenia) are the main indications/indicators for dose adjustment. Over 10% of patients withdraw from treatment because of side effects.(17) Flu like symptoms and fever can be treated with paracetamol. To further improve compliance, erythropoietin can be given for anaemia and antidepressants (in particular SSRIs) for psychiatric symptoms.

Future therapies for Hepatitis C

The development of new antiviral drugs is of particular importance for those patients who did not achieve a sustained response to combination therapy. Recently HCV protease and polymerase inhibitors have been developed and tested in phase II clinical trials in patients with HCV, including small molecule inhibitors of the HCV NS3 serine protease and NS5B RNA-dependent RNA polymerase.(18) One of the most promising new antiviral drugs is VX-950, a HCV NS3.4 protease inhibitor. Currently large phase 3 studies are underway. (19)

Follow up

Patients with haemophilia and chronic hepatitis C must be checked regularly. In follow up blood samples for liver enzyme tests (ALT and gamma GT), alfa foeto protein, thrombocyte count and Prothrombin time are taken to estimate the progression of liver disease. Ultrasound may be useful to detect liver failure (ascites, abnormal vascular structures and blood flow) or liver carcinoma.

Transient Elastography (Fibroscan®) is a non-invasive method for the assessment of liver fibrosis.(20) It is a good alternative for liver biopsies which in haemophilia patients are expensive because of the required clotting factor correction and are relatively contra-indicated because of increased bleeding risks.

Follow up	ALT, gamma GT, thrombocyte count	Prothrombin time, alfa foeto-protein	Transient elastography	Ultrasound
frequency	2 x year	1 x year	once in 2 years	once in 3 years

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Chapter 6. Inhibitors in the elderly haemophiliac

F.W.G. Leebeek

Introduction

Inhibitors against factor VIII (FVIII) are a major problem in the treatment of patients with haemophilia. The cumulative risk of inhibitor development in severe haemophiliacs reaches 30-35% in several studies.(1,2) Most inhibitors develop early in children with severe haemophilia within the first 50 factor VIII exposure days.(1) Inhibitors are less frequently seen in patients with mild haemophilia, and develop mostly in adulthood.(3) In these patients endogenous FVIII, although dysfunctional, is still synthesized and present in the circulation. Therefore the administered exogenous factor VIII may be less immunogenic. In addition it may require an anamnestic response to detect inhibitory antibodies. Several factors may play a role in inhibitor development, such as specific mutations in the A2 and C2 domain of the FVIII gene, intensive treatment periods, continuous infusion, and product characteristics.(4,5)

Nowadays treatment of bleeding in patients with high titre inhibitors usually consists of infusion of activated prothrombin complex (APCC) or recombinant factor VIIa. Although these regimens are both effective in the majority of patients, side effects such as thrombotic events have been reported. Because factor VIII inhibitors are only rarely seen in elderly patients, studies on the treatment of these patients, who may even be at higher risk of developing thrombotic complications, is limited. Illustrated by a case history of an elderly haemophiliac who developed high titre inhibitor to FVIII, the course and treatment of inhibitors in elderly patients will be discussed.

Case History

The history of a 69 year old male with mild haemophilia (FVIII level 0.07 U/ml) revealed a near fatal bleeding after tonsillectomy in childhood and severe bleedings after tooth extractions. He did not have any bleeding problems in the following years, and underwent no surgical procedures. During the last few years, he had a knee bleeding after minor trauma and a bleeding after dental extraction, for which he received recombinant factor VIII on both occasions.

He complained of prostate related problems, and a prostate biopsy was performed. Because of urinary retention a catheter was placed and removed several weeks later. During these interventions he was treated with recombinant factor VIII, with adequate recoveries and good clinical effect. Because of recurrent retention due to severe prostate hyperplasia, a radical prostatectomy was scheduled.

At preoperative screening he had a low titre inhibitor to FVIII of 1 BU/ml. His FVIII level was 0.08 IU/ml. He had no spontaneous bleeding. In his family no patients with haemophilia A ever developed inhibitors. Prior to surgery a dose of 50 IU FVIII/kg was administered, with a recovery of only 0.44 IU/ml. He was given high-dose factor VIII during the peri-operative period. Within a few days the inhibitor titre rose to a maximum of 70 BU/ml. He was given desmopressin (0.3 μg/kg i.v.), which resulted in a rise of FVIII from 0.06 IU/ml to 0.15 IU/ml. Therefore he was treated with recombinant factor VIIa (rFVIIa) (bolus infusion of 90 μg/kg, followed by continuous infusion at a rate of 17 μg/kg/hour) during day 6-9 after surgery.

No bleeding occurred during surgery and the post-operative days. Despite the high titre inhibitor his FVIII levels remained around 0.09 IU/ml. After the surgical intervention he did not have any bleeding complications for several years. Therefore no immune tolerance treatment was started.
The inhibitor titre decreased gradually and was not measurable 6 months after the initial detection of the inhibitor.
Three years later the patient presented with a muscle bleed after trauma. He was treated with a total of three bolus injections FVIII concentrate over two days. He again developed an inhibitor with a maximum rise of 122 BU/ml. After two years this inhibitor is still detectable (10 BU/ml). In case of bleeding he is treated with rFVIIa.

Development of inhibitors in elderly patients

Inhibitors to factor VIII are predominantly seen in young children who have recently started therapeutic treatment with clotting factor concentrates. Inhibitors are only rarely seen late in life and mainly in patients with mild haemophilia as presented in the case of our patient. The development of inhibitors in patients of this age is probably caused by the fact that these patients did not previously receive many factor VIII infusions. In their youth, if they suffered several bleeding episodes, treatment with factor VIII concentrates was not available. During adulthood they did not experience severe bleeding episodes and did not undergo surgery. At an advanced age, however, these patients encounter age-related health problems, which necessitate intervention and even surgery. Patients then receive FVIII treatment for a prolonged period. This may be for the first time in their life. Apparently in these cases inhibitors may develop and therefore must be carefully monitored regularly, especially before planned surgical interventions. Also, during the course of treatment for bleeding or surgery, recoveries should be measured regularly.

Factors in inhibitor development

In recent years several factors predisposing to inhibitor development in mild haemophilia have been identified, including several mutations in the FVIII gene especially in the A2 and C2 domain.(5,6) It would be of interest to perform mutation analysis also in elderly patients to investigate a relationship with inhibitor formation. In our patient the inhibitor was detected after only a limited number of treatment episodes of FVIII, however given at a regularly basis, i.c. once every six weeks in case of bladder catheter change. Our patient was not treated with continuous infusion of factor VIII prior to development of the inhibitor.

Treatment

Bleeding episodes in haemophilia patients with high titre inhibitors are normally treated with activated coagulation factors, such as activated prothrombin complex (APCC, FEIBA®,) or recombinant factor VIIa (rFVIIa) Novoseven®,) in case of bleeding or surgery. One of the potential side-effects of this treatment is the occurrence of venous and arterial thrombotic events, as have been described before.(7) There is a lot of experience with APCC and rFVIIa in younger patients with inhibitors, but information on the treatment of elderly hereditary haemophilia patients (>75 years) is still limited.(8) Patients with acquired haemophilia who are mostly also in the advanced age group have been successfully treated with rFVIIa or APCC.(9)

Desmopressin

Patients with mild haemophilia with inhibitors in whom the antibodies are not directed at the patients native FVIII can sometimes be treated with desmopressin (DDAVP).(5) In our patient no decrease of factor VIII activity was seen despite the presence of the high inhibitor titre to factor VIII, indicating that the inhibitor was only directed towards exogenous FVIII. In elderly patients the use of desmopressin may be contra-indicated because of co-existing coronary artery disease. Acute myocardial infarction has been reported after desmopressin infusion.(10) In addition the use of desmopressin is limited in haemophilia patients with a FVIII level of at least 0.05-0.08 IU/ml, because the maximum rise in factor VIII is only two- to three-fold following desmopressin.(10) Our patient responded only marginally to DDAVP (max. rise to 0.15 U/ml). The patient was successfully treated with high dose FVIII and later with rFVIIa (90 μg/kg bolus followed by continuous infusion for three days). No side-effects of treatment with recombinant factor VIIa were seen.(11)

Anamnestic response

Mild haemophilia patients in whom the inhibitor is also directed towards their own factor VIII, can be treated with immune tolerance induction.(12) In our patient no immune tolerance therapy was initiated, because the patient did not experience spontaneous bleeding episodes, and FVIII levels remained around their baseline levels of 0.05-0.10 IU/ml. Recently rituximab (anti-CD-20) has been used to treat patients with hereditary haemophilia with inhibitors. So far only two elderly patients (65 or older) have been reported and showed different responses to rituximab.(13) In the majority of mild haemophilia A patients with inhibitors, the inhibitor will disappear spontaneously over time, as was also seen in our patient.(3) Upon renewed treatment with coagulation factor concentrate an anamnestic response will occur and the patient again will develop an inhibitor. It may therefore be more appropriate to treat a bleeding episode with rFVIIa to avoid this anamnestic response.

Conclusion

The case presented demonstrates that a haemophilia consultant should always be aware of the risk of inhibitor development in an elderly patient with mild haemophilia. These patients may pose an additional problem because limited information is available on the treatment of this specific patient group. Treatment with bypassing agents or DDAVP can be instituted and was effective in our patient.

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Chapter 7. Cardio-vascular disease

K. Peerlinck

Introduction

In the developed world atherosclerotic vascular disease (heart disease and stroke), is the leading cause of death accounting for 41% of all deaths. Coronary heart disease is the most lethal of the atherosclerotic vascular diseases. Mortality rates for this disease rise steeply with age and reach major proportions after the age of 55 years. Mortality rates are higher among men than women. The mortality rate reported for coronary disease in the USA is 79.4/100.000.(1) From the Framingham study it can be estimated that the average annual rates of first cardiovascular events increases from 7/1000 at the ages of 35-64 years to 68/1000 at the ages of 65-94 years.

Atherosclerotic lesions begin as small collections of macrophages and macrophages filled with lipid droplets (foam cells) accumulate in the intima at susceptible sites of the arterial system. Such changes are already present in infants and older children but in many they do not develop further. In people with high risk factors for atherosclerosis, extra-cellular lipid and more foam cells continue to accumulate until the normal cell and intercellular matrix structure of the intima disintegrates. The surface of a lesion may then become disrupted, blood may accumulate below the surface and thrombi may form on the surface. As a consequence, reparative increases in smooth muscle cells and fibrous connective tissue may then accelerate wall thickening and lumen narrowing.(2)
The major modifiable risk factors contributing to the occurrence of atherosclerotic disease are smoking, high plasma total cholesterol, hypertension, obesity and diabetes.

Atherosclerosis is rarely fatal in itself. It is the occurrence of complicating thrombosis, usually precipitated by sudden rupture of the plaque surface, that turns benign atherosclerosis into malignant atherothrombosis. The main event responsible for acute coronary syndromes (unstable angina, myocardial infarction, and sudden coronary death) is plaque rupture with superimposed thrombosis. The thrombotic response to plaque rupture or erosion depends on three major determinants:
(a) the character and amount of exposed plaque components (local thrombogenic substrate);
(b) the degree of stenosis and surface irregularities (local flow disturbances);
(c) thrombotic-thrombolytic equilibrium at the time of plaque rupture or erosion (systemic thrombotic propensity).(3)

The importance of the thrombotic-thrombolytic equilibrium in determining the outcome at plaque rupture or erosion is documented by the protective effect of anti-platelet and anticoagulant agents against acute coronary syndromes in patients with ischaemic heart disease and by the prothrombotic effect of high levels of fibrinogen, factor VII, factor VIII, elevated levels of plasma tissue factor and other haemostatic determinants.

Ischaemic heart disease in haemophilia

Death from ischaemic heart disease is lower in patients with haemophilia than in the general age-matched male population. This has been first documented in a Dutch survey on mortality and causes of death in Dutch haemophiliacs, 1973-86 (4) and was confirmed in the prospective cohort study in the Netherlands over the period 1992-2001.(5) Similar lower mortality from ischaemic heart disease has also been confirmed in the US.(6) These data have been interpreted as providing evidence that a hypocoagulable state offers protection from the final thrombotic event that precipitates infarction. It is still unsolved whether haemophilia also offers protection from the development of atherosclerosis. The presence of extensive atherosclerosis in a haemophiliac was described as early as 1957.(7) This patient, who appeared to have moderately severe haemophilia, had typical angina pectoris at age 73. Post-mortem examination (patient died at age 76 of intractable melena) showed extensive coronary and aortic atheroma.

In atherosclerosis-prone mice, factor VIII deficiency led to dramatically reduced early stage atherosclerotic lesions with an aberrant composition (almost devoid of fibrinogen and platelets). At a later stage, the absence of factor VIII delayed disease progression but did not lead to a difference in lesion composition but rather induced a delay in disease progression.(8) Using B-mode ultrasonography to quantify early atherosclerotic vessel-wall changes to quantify intima-media thickness in the carotid and femoral arteries Dutch researchers concluded that hypocoagulability caused by haemophilia or von Willebrand disease has at most a limited effect on atherogenesis.(9) Only in the subgroup with moderate to severe haemophilia was intima-media thinner as compared to controls. By contrast a clear effect of established risk factors (age, smoking, hypertension, hyperlipidemia, diabetes) on intima-media thickness was found in this study.

Although in animal models an impact of (complete) factor VIII deficiency on the development of atherosclerosis is documented, this protective effect seems to be minimal in patients. The decreased mortality of ischaemic heart disease is probably caused by a decreased tendency to form occluding clots.

Case: an acute anteroseptal infarction

A 72-year old patient with severe haemophilia A (10) and longstanding high titre anti-factor VIII antibodies was hospitalized for dental extractions. He was previously treated on several occasions with FEIBA® with or without tranexamic acid for bleeding episodes or minor interventions. He had no history of angina pectoris. He had been a cigarette smoker for many years and was treated for hypertension. His lipid profile was normal. He received recombinant factor VIIa (rFVIIa) (102 µg/kg bodyweight) prior to dental extraction under local anaesthesia. At the end of the procedure the patient felt unwell, with nausea and retrosternal discomfort. An electrocardiogram showed signs of an extended acute anteroseptal infarction. Emergency coronarography showed complete proximal occlusion of the left anterior descending coronary artery and diffuse atheroma of the right coronary artery with multiple stenoses up to 50%. Emergency percutaneous transluminal angioplasty (PTCA) of the occluded left coronary artery was performed with uncomplicated restoration of patency followed by stenting. During PTCA a single bolus injection of 10 000 U of unfractionated heparin was given and aspirin was started. Approximately 18 hours later the catheter sheath was removed from the right femoral artery, preceded by a bolus injection of rFVIIa (68 µg/kg; 4.8 mg), followed after 3 hours with the same dose. Haemostasis was excellent initially, but approximately 68 hours after the last dose, a large haematoma developed in the right groin with blood pressure and haemoglobin fall; treatment with rFVIIa was reinstituted at a dosage

of 4.8 mg every 6 hours for five days, two units of packed cells were transfused and aspirin was stopped. No further complications occurred.

Epilogue

Four years after his myocardial infarction a right colon cancer was diagnosed. A hemicolectomy was performed using rFVIIa without any adverse event. Unfortunately the patient died from liver metastasis two years later, aged 78. He never had any new cardiac complaints.

Management of cardiovascular disease in haemophilia

Extensive guidelines based on high levels of evidence exist for the prevention and treatment of cardiovascular disease in the non-haemophiliac population. However, no such guidelines for patients with coagulation disorders can be found. As a consequence of the near normal life expectancy for patients with haemophilia more patients present with cardiovascular diseases and their complications. An important collaborative effort will be needed to develop evidence based guidelines for this group. In the next paragraph suggestions for management will be made.

Prevention of atherosclerosis

Prevention and treatment of the established risk factors should be instituted as in the non-haemophilic population. Patients should be urged not to start or to quit smoking. Hypertension, hyperlipidemia and diabetes should be screened for and treated as in the non-haemophilic population. Reduction of obesity should be aimed at. Physical activity should be stimulated and suitable exercise programmes offered to those with physical disabilities.

Management of haemophilia during cardiac interventions

Few case reports have been published on the management of haemophilia during percutaneous coronary interventions.(11-15) Basically in all published cases, during the procedure, factor levels are restored to haemostatic levels and anticoagulation and anti-platelet therapy are given as in patients without bleeding disorders. The same principles are followed in case of open heart surgery. Haemostatic levels of coagulation factors can be maintained using continuous infusion or repetitive bolus injections. If valve replacement is necessary bioprotheses are preferred, since they do not require lifelong anticoagulation.

Use of anti-platelet agents

Low dose aspirin (80-160 mg) and/or clopidogrel are widely used in the secondary prevention of cardiovascular disease. No published data are available for haemophilia patients.
Low dose aspirin is generally well tolerated in patients with mild/moderate haemophilia and in most patients with severe haemophilia. Few patients develop unacceptable bleeding during treatment with low dose aspirin, even when they are not on prophylaxis with clotting factors. In my institution low dose aspirin is started for secondary cardiovascular prevention and is withdrawn in those patients with unacceptable bleeding.
To prevent restenosis after coronary stenting, treatment with clopidogrel is given. Again, clopidogrel is generally well tolerated in mild haemophilia. In patients with severe haemophilia we generally give prophylaxis with factor VIII or IX concentrates.

Conclusions

With an increasing age of our haemophilia populations cardiovascular diseases and their treatment become more prominent. Although some protection from atherosclerosis may be present in this population (maybe dependent on the degree of severity and the amount of life-time treatment), atheroma does develop and is dependent, as in non-haemophiliacs, on reversible risk factors such as smoking, hypertension, hyperlipidemia, diabetes and obesity. Prevention of atherosclerosis in our haemophilia population is thus mandatory. Mortality from cardiovascular disease is lower in the haemophilia population, probably reflecting protection from the development of fatal occlusive thrombi. However, with increasing treatment with clotting factor concentrates this 'advantage' might also diminish, even disappear. Data are needed on the risk/benefit of secondary prevention with anti-platelet agents in this vulnerable population.

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A tragedy in the seventies[1]

A male born in 1957 was identified in 1958 to have severe haemophilia A, factor VIII <1%. He received prophylactic factor VIII three times a week because of recurrent joint bleedings. After age three he experienced frequent haematuria. One year later a large swelling in the left abdomen was found. There was no production of urine and the patient had hypertension. This complication begun after the patient was treated with tranexamic acid during haematuria. At radiological examination the diagnosis of bilateral hydronephrosis was established. The kidney function changed for the better.
In the following six years he continued to have haematuria. Hydronephrosis on both sides, and a non-functioning left kidney were found. The endogenous creatinin clearance was 100 ml/hour. This was reason for an expectative management.
One year later, in 1975, he had an accident. He felt from his moped and the handlebar of the moped injured his abdomen. He had pain in the abdomen and thorax, he was vomiting and a profuse haematuria occurred. Blood pressure was 80/90 mmHg. His haemoglobin level fell to 4.1 and later 2.0 mmol/l. He was treated with factor VIII concentrate, and blood transfusion and laparotomy were performed. The left kidney and the spleen were completely destroyed and had to be removed. The total blood loss was 7.5 l. Factor VIII was kept above 50%. Post-operatively the urine production stopped and finally also the right kidney had to be removed because of arterial bleeding. The patient was put on dialysis 3 times a week. Factor VIII was given shortly before dialysis and the dialysis was uneventful.
In December 1976 kidney transplantation with a cadaver kidney was performed. There was a direct diuresis post-operatively and 3 weeks later the endogenous creatinin clearance (ECC) was 70 ml/hour. In August 1977 proteinuria developed and in November 1977 he was treated with anti-rejection therapy with corticosteroids, later with prednisone and Imuran®.
In August 1978 he became seriously ill with melena and blood loss *per anum*. At examination ileus was diagnosed. At laparotomy, a Meckels diverticle and bleeding in the small intestine were found. Postoperatively, a Pseudomonas and Clostridium infection developed in the wound. Despite the intensive treatment the patient died, 21 years old.
This case shows how difficult it used to be to treat a severe injury in a patient with haemophilia.

[1] Case by I. Novakova

Chapter 8. Invasive diagnostics and surgical interventions

K. Meijer & J. van der Meer

Introduction

The principles of factor replacement therapy for interventions are the same in older and younger haemophilia patients. However, the prevalence of co-morbidity is higher in older patients and the spectrum of diagnostic and therapeutic interventions is different. Co-morbidity includes orthopaedic limitations, viral infections, cardiovascular disease and internal diseases, as discussed elsewhere in this book. Within the scope of this chapter, advanced liver disease with decreased synthetic function and thrombocytopenia must be considered, causing additional haemostatic abnormalities. Patients with mild haemophilia and prominent cardiovascular disease may be using drugs that interfere with platelet function. On the other hand, elderly patients in whom the coagulation defect is corrected may be at increased risk of thrombotic complications.(1)
In this chapter, after some general remarks, we focus on interventions for urological conditions, on gastrointestinal endoscopy, liver biopsy, dermatological procedures and surgery for malignancy. The available literature is summarised and recommendations are given. Often, no definite data are available and recommendations are based on experience.

General remarks

Patients with chronic illness have an increased risk of depression and other psychiatric co-morbidity. In an elderly population, this may have an atypical presentation. In the context of interventions, there is risk of delirium, which may lead to injuries and bleeding in patients with haemophilia.
As in younger patients, the presence of an inhibitor must be excluded before surgery, and the preoperative level of factor VIII or IX must be measured. For all surgery that causes immobility or after which patients are admitted to hospital, elastic stockings must be prescribed both intra- and postoperatively. In major surgery in elderly patients, we start pharmacological thrombosis prophylaxis (low molecular weight heparin) once haemostasis is definitively achieved, mostly on the day after surgery. This is continued as long as suppletion is aimed at factor levels at or above 50%.

Interventions for urological conditions

In the general population, urological interventions have a high frequency of bleeding complications. Literature on such procedures in haemophilia patients is available, but consists mainly of case reports. We will provide information on circumcision for medical reasons, transurethral resection (TUR) of the prostate, prostate biopsy, surgery for prostate and for bladder cancer.
There is doubt about the effectiveness of desmopressin in urological interventions: In one series of different procedures in five mild haemophilia patients, four had bleeding complications despite adequate levels of factor VIII after the administration of desmopressin.(2)

Circumcision for medical reasons
Most data on circumcision are from children. In a small, controlled trial, continuous factor concentrate for two days plus the use of fibrin glue was effective.(3) However, fibrin glue is derived from plasma and has been implicated in the formation of anti-factor V antibodies. We do not use fibrin glue for this indication.

Prostate biopsy
No data are available. In the general population, prostate biopsy causes mild to moderate haematuria in the majority of patients. Some also report rectal bleeding.

Transurethral resection (TUR) of the prostate
Haematuria may persist for up to six weeks in patients without coagulation abnormalities. In haemophilia, no data are available. In the general population, the use of tranexamic acid reduces blood loss.(4)

Surgery for prostate cancer
No data on radical prostatectomy are available beyond a report of an uncomplicated case. In the general population, the incidence of bleeding complications is low. In contrast, the risk of intestinal bleeding as late toxicity of curative radiotherapy is significant.(5) This must be taken into account when planning treatment for prostate cancer in patients with haemophilia: surgery may be preferable over radiotherapy.

Case: Resection of bladder carcinoma

Mr U. is a 57-year-old patient with haemophilia B and cirrhosis caused by hepatitis C. He was admitted for transurethral resection of a localised bladder carcinoma. His platelet count was 47. A preoperative bolus of a recombinant factor IX concentrate was given, followed by a continuous infusion, both aimed at 100% factor IX levels. The thrombocytopenia was accepted, as it was considered caused by splenic pooling.
The procedure, including additional random biopsies, was uncomplicated. Postoperatively, the factor IX level had fallen to 67%. The next four days, factor IX levels were kept around 90% and the patient made an uneventful recovery. He was discharged home with a daily dose of 1000 IU of factor IX concentrate for another four days. After that he would return to his prophylactic regimen of 1000 IU twice weekly.
Three weeks after surgery, he presented with ongoing haematuria, passing of clots and difficulty voiding, despite additional treatment with factor IX concentrate. Haematuria did not resolve until six weeks after surgery. At that time, iron deficiency anaemia had developed.

This case taught us that, after haemostasis seems to be secured in the days after resection, late bleeding can be a problem and that even without the use of antifibrinolytic drugs, symptomatic clots can be formed.

Recommendations for urological conditions

Circumcision for medical reasons
Perform circumcision in an in-patient setting.
Preoperative factor concentrate bolus aimed at 50%, followed by continuous infusion aimed at a level of 50% for two days.

Prostate biopsy
Perform biopsy in an in-patient setting.
Preoperative factor concentrate bolus aimed at 50%, followed by continuous infusion aimed at a level of 50% for two days.
Tranexamic acid 2 g three times daily on the day of, and the day after surgery. Use elastical stockings.

Transurethral resection (TUR) of the prostate
Preoperative factor concentrate bolus aimed at 100%, followed by continuous infusion aimed at a level of 70% for three days and 50% for four days.
Tranexamic acid 2 g three times daily on the day of, and for a week after surgery. Be sure to use elastical stockings, as tranexamic acid may increase the risk of deep vein thrombosis. If in the weeks after surgery haematuria recurs, tranexamic acid can be restarted.
Fluid intake and diuresis must be adequate.

Surgery for prostate cancer
Preoperative factor concentrate bolus aimed at 100%, followed by continuous infusion aimed at a level of 70% for three days and 50% for four days.
Use elastical stockings preoperatively and until the patient is fully mobilised.
In addition, consider low molecular weight heparin (LMWH) for thrombosis prophylaxis. LMWH is started postoperatively, if haemostasis is secured and continued for the period that factor levels are aimed >50%.

Gastrointestinal endoscopy and colonscopy

The main indications for upper gastrointestinal endoscopy are acid related disease and diagnosis or treatment of oesophageal varices which are seen in patients with chronic hepatitis C infection. Clinical experience with these procedures in haemophilia patients is ample, but publications are scarce.
Diagnostic upper gastrointestinal endoscopy can be performed as an outpatient procedure. A single factor concentrate bolus aimed at 50% is sufficient.(6) Data on the treatment of varices are not available.

Recommendations for gastrointestinal endoscopy and colonscopy

Endoscopy
Preoperative factor concentrate bolus aimed at 50%. If no biopsies are taken, discharge. If biopsies have been taken, local haemostasis must be secured. Repeat the bolus for factor VIII concentrate after 12 hours and observe overnight. If the patient is stable, he can be discharged the next day. Depending on the aspect of the lesion(s) and the size and number of biopsies, continu factor concentrate boluses.
For endoscopic treatment of varices, we give a pre-procedure factor concentrate bolus aimed at 50%. For FVIII, this is repeated in the evening. Patients are observed overnight and, if the procedure was uncomplicated and they remain stable, are discharged the next day.

Colonoscopy
Similar to those in diagnostic upper gastrointestinal endoscopy.

The role of non-steroidal anti-inflammatory drugs in the prevention of colon carcinoma is being investigated. Their efficacy does not seem so high that it offsets the contra-indication in patients with haemophilia.

Liver biopsy

The main indication for liver biopsy in haemophilia patients is chronic hepatitis C infection. There is no consensus that biopsy must be performed in all patients: most centres, including ours, manage hepatitis C without biopsy. Guidelines for treatment are not based on histology. There is controversy about the safety of percutaneous liver biopsy in haemophilia patients. An old retrospective study reported significant bleeding in 12.5% of patients, but no deaths. From unpublished data, a 1% mortality rate was estimated.(7)
A more recent case series reported no complications in 22 laparoscopic liver biopsies.(6) Prior to the procedure, they excluded the presence of an inhibitor. A factor concentrate bolus aimed at a level of 100% (factor VIII) or 70% (factor IX) was given. Post-procedure, levels were kept at 50-100 and 50-70%, respectively, for two days. Factor concentrates were continued for a total of four days. No more details were given.
A number of studies on transjugular biopsies in haemophilia patients have been reported. The largest series describes 65 patients, with significant bleeding in 1 (1.4%).(8) They gave a pre-procedure factor concentrate bolus aimed at a level of 75-100%. Post-procedure, patients were discharged. They repeated bolus injections at home every 12 hours for two days, aiming at trough levels of 50%.
More recently a non-invasive method to assess liver fibrosis has been introduced. Transient Elastography (Fibroscan®) is a good alternative for live biopsies with comparable results.(9)

Recommendation for liver biopsy

Discuss the indication for liver biopsy with the hepatologist. If technically feasible, the transjugular approach is preferred.
Perform as an in-patient procedure: preoperative factor concentrate bolus aimed at 100%, followed by continuous infusion aimed at a level of 50% for two days.

Other hepatitis C related procedures

Case: Radiofrequency ablation of hepatocellular carcinoma

Mr V. is a 51 year old patient with severe haemophilia A. He has chronic hepatitis C, genotype 2. In 1998, ultrasonography was indicative of cirrhosis. He declined antiviral therapy until 2005. Treatment with PEG-IFN and ribavirin was then complicated by neutropenia and thrombocytopenia, necessitating dose reductions. He had no virological response. During follow up, hepatocellular carcinoma developed.
After a complete evaluation, he was placed on the waiting list for orthotopic liver transplantation (OLT). To halt the progression of the carcinoma until a donor liver became available, percutaneous radiofrequency ablation was planned. (In radiofrequency ablation, an electrode is placed in the tumour. An alternating current heats the tumour cells and causes necrosis.) Factor VIII levels were kept between 80-100% during the procedure and the next two days. After that, levels were kept at about 50% for another three days. There were no bleeding complications. The patient did, however, have a lasting discomfort at the site of the puncture. A repeat CT scan showed no suspicious lesions.

Orthotopic liver transplantation

Haemophilia is not a contra-indication to orthotopic liver transplantation (OLT). The main indication in haemophilia patients is end stage liver disease or hepatocellular carcinoma due to chronic hepatitis C. Haemophilia itself is not considered an indication for OLT, but OLT does cure both haemophilia A and B.
Our protocol for liver transplantation calls for notification of the physician on call for the Haemophilia Centre at the moment a donor liver is available. He/she coordinates the communication with the coagulation laboratory and is responsible for the dosing of factor concentrate. A preoperative factor concentrate bolus aimed at 100% is given, followed by continuous infusion aimed at a level of 100% throughout surgery. Factor levels are measured at least at the start of surgery and at the end of every phase of the OLT (pre-anhepatic, anhepatic, post-anhepatic), and if blood loss is more than expected. Post-operatively, factor levels are measured twice daily. As the donor liver starts to synthesize factor VIII of IX, suppletion can be tapered. Per-operatively, we use compression stockings. Post-operatively, the standard regimen of thrombosis prophylaxis in the OLT programme is used.

Dermatological procedures

No data are available besides a small number of case reports on bleeding complications. Bleeding has also been described after dermatological cryosurgery.

Recommendation:
For excisions, cryosurgery and the scraping of seborrhoeic (‘senile’) warts a single factor concentrate bolus aimed at 30-50% is sufficient, if local haemostasis is secured.

Cataract extraction

Published data are case reports in patients with either an inhibitor or with previously undiagnosed haemophilia. In the general population, the risk of bleeding after cataract extraction is very low. In non-haemophilia patients who use oral anticoagulation, this does not have to be interrupted.

Recommendation:
Discuss preference for topical anaesthesia with ophthalmologist. Use single pre-operative factor concentrate bolus aimed at 50%, and observe overnight.

Surgery for malignancy

Suppletion therapy is highly dependent on the nature and extent of surgery. However, patients whose haemophilia is fully corrected and who have active malignancy and undergo surgery, may be at increased risk for thrombotic complications.(1) In such cases, as in major orthopaedic surgery, we use low molecular weight heparin (LMWH) for thrombosis prophylaxis. LMWH is started postoperatively, if haemostasis is secured and continued for the period that we aim at factor levels >50%. After this period, we stop the LMWH (as opposed to the general population, in which extended thrombosis prophylaxis after oncological surgery is indicated). In addition to pharmacological thrombosis prophylaxis, compression stockings should be used per-operatively and until the patient is fully mobilised.

Case: Surgery for carcinoma of the lung

Mr W. is a 87-year-old patient with mild haemophilia B (factor IX 7%). He has a history of coronary heart disease and mild COPD. He was hospitalized for analysis of an abnormal chest X-ray. Bronchoscopy, performed after the administration of a 4000 U of a recombinant factor IX concentrate (rFIX), showed no abnormities. A right lower lobectomy was performed and histological examination confirmed the diagnosis of a T2N0M0 squamous cell carcinoma of the lung. Per- and post-operatively, adequate suppletion of rFIX was given.
No bleeding complications, apart from a flank haematoma, occurred. The immediate post-operative recovery was complicated by delirium. After discharge, it took more than a year before the patient had recovered to a stable level of performance. He did not recover to his usual health and activities. This was a very frustrating period for the patient. In this year, he needed factor IX suppletion for a number of falls and was progressively hindered by arthropathies.

Immobilization

Pain and functional limitations due to arthropathy often increase when patients are immobilized after surgery. In elderly patients, prolonged immobilization can lead to irreversible loss of function. Early mobilization is the most important intervention. If this is not possible, the help from an experienced physical therapist is needed to prevent further disability.

Psychiatric complications

Patients with chronic illness have an increased risk of depression and other psychiatric co-morbidity. In an elderly population, this may have an atypical presentation, including cognitive impairment. Medical staff must be aware that a number of drugs that are mainly prescribed to the elderly (including benzodiazepines and beta blockers) can cause depressions.(10) When depression is suspected, psychiatric consultation must be sought.
In the context of interventions, there is risk of delirium. The incidence of post-operative delirium in older patients is 15 to 50%, and delirium is associated with increased mortality.(11) In patients with haemophilia, delirium may lead to injuries and bleeding. The most important intervention is an early diagnosis. Both medical and nursing staff must be aware of the high incidence of this complication. Patients with risk factors (including pain, hypoxia, infection, sleep deprivation, drugs) must be monitored for early signs and symptoms, and geriatric consultation must be considered. For symptomatic treatment, we use 2 mg of haloperidol daily and 10 mg of temazepam at 10 pm.(12)

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A case from Norway[2]

This story is about a 62 year old man with severe haemophilia A. As a child he had a high bleeding tendency, first of all in his ankles and knees, but his elbows and shoulders were affected too and he had many muscle bleeds. That meant many days in hospital or at home in bed with swelling and pain waiting for the bleeding to stop. Despite many haemorrhages his parents let him play like other children and even today, with prosthesis and limited movement, he is grateful for that! He does not wish they had made any different choices for him, which he is certain, would have turned him into a spoilt and fearful man!
In 1978 he started on demand treatment, but his adherence to treatment was often poor. Over the years he developed severe arthropathies and had joint replacements and arthrodeses in several joints. The many bleeding episodes had also led to many missed days at school and his education was poor. He wanted to live as normal a life as possible and in spite of insufficient education he found a job and after some time even had his own small store. He married and he and his wife bought an apartment. They had two children and lived more or less like any other family until 2003.

In 2003 he had a severe intra-cerebral haemorrhage. His wife called for an ambulance which arrived promptly but the paramedics refused to take him to the National hospital where there were experts on haemophilia treatment. Instead they took him to the local hospital and only after his wife had made a terrible scene, he was transferred to the National hospital. Immediately upon arrival he had surgery and the haematoma was evacuated. He survived and was transferred to the rehabilitation department a few weeks later. He started physiotherapy and was slowly recovering when he fell out off bed and fractured his femur which required a new operation. He then returned to the rehabilitation department and resumed training. After a few weeks he thought he had a severe muscle bleed but further examination revealed cancer. Once again he had to have surgery followed by a third period in the rehabilitation department.

After a few months of intensive physiotherapy and training he finally returned home. But now he needed help. He was no longer able to take care of his home treatment. So his wife had to learn and take over prophylactic infusion of clotting factor concentrates until he will be able to do it himself again. His wife has a full time job so for three hours per week someone comes in to help him with the shopping and drive him to and from physiotherapy, because he can no longer drive himself. He has an elevator, uses crutches inside the house and a wheelchair outside. One of his goals is to be able to use crutches outside too. Since he cannot work he receives disability benefits through the national insurance. He is now living with his family and is surely but slowly doing better and gradually growing more independent. That he actually has managed to achieve all this, is the result of good co-operation between him, his wife and various professionals like his doctor, nurse, physiotherapist, social worker, occupational therapist and psychologist.

[2] Case by Siri Grønhaug

Chapter 9. Internal diseases

I. Novakova

Introduction

Morbidity and mortality of haemophilia patients in the period before the introduction of treatment with clotting factors was mainly determined by the severity of the haemorrhages. The mean life expectancy of people with haemophilia at the time was less than 30 years.(1) Therefore, diseases more often associated with increasing age like hypertension, diabetes mellitus type 2, overweight, cardiovascular diseases and renal failure were not seen as an important issue in this population. In the last 40 years treatment possibilities improved considerably and consequently life expectancy of haemophilia patients increased till the 1980s. Then mortality increased again due to the acquired immunodeficiency syndrome (AIDS) caused by contaminated blood products.
Chronic liver disease and hepatocellular carcinoma are the other important causes of death, which will influence the mortality rate even in the coming years. At this moment, the overall mortality of people with severe haemophilia is 5-fold higher than in men in the general population.(2, 3) In HIV and HCV free patients the rate of death is reported to be slightly higher than expected (2) or comparable with the general population.(4) Fatal haemorrhages and presence of inhibitor against a clotting factor still contribute to the death of some patients.

Renal disease

The potential causes of renal disease in haemophilia are kidney bleedings, HIV infection, use of drugs as tranexamic acid and immune tolerance induction in haemophilia B with inhibitors to factor IX. Furthermore, in elderly haemophiliacs kidney function impairment due to hypertension and diabetes can occur comparable to the general population.
Haematuria is a common symptom in severe haemophilia and mostly there is no clear evidence for association with renal failure, apart from severe kidney trauma. A possible association between kidney bleedings and hypertension has been reported.(5)
Tranexamic acid has antifibrinolytic activity through blocking the lysine binding site on plasminogen, which is essential for binding to fibrin. The drug enters the extra vascular space and accumulates in the tissues. This leads to the inhibition of tissue fibrinolysis. It is a widely used drug in different bleeding disorders such as haemophilia, von Willebrand disease, menorrhagia, gastrointestinal bleedings and others. Cases of thrombotic complications have been described but these complications are uncommon.(6) Treatment given during haematuria may cause an acute renal obstruction. A case of acute renal cortical necrosis caused by tranexamic acid has been reported,(7) but it is a rare complication.
The prevalence of renal disease in HIV infection varies between 2% and 10%. The most common renal disorder in HIV is HIV associated nephropathy (HIVAN), caused by direct viral infection. Highly active antiretroviral therapy (HAART) reduces the incidence of HIVAN. Some other antiretroviral and antifungal drugs yield a nephrotoxic effect. The other renal diseases associated with HIV include immunoglobulin A nephropathy, cryoglobulinemia, amyloidosis and a lupus like immune complex glomerulopathy.(8)
About 30% of Immune Tolerance Induction (ITI) therapy for inhibitor to factor IX in haemophilia B is complicated by the development of nephrotic syndrome. This complication

sometimes improves after stopping the therapy with factor IX concentrate. Nephrotic syndrome as a complication of ITI has not been described in haemophilia A patients.(9)

Risk factors for infections

Case: hepatitis C and liver cirrhosis
A male born in 1947 was diagnosed at age three to have moderate haemophilia A, factor VIII 2%. He experienced more recurrent joint bleedings than expected in moderate haemophilia. Treatment with cryoprecipitate, and later with factor VIII concentrate had been given regularly for his bleedings. In 1975 chronic hepatitis was diagnosed. In 1977 he developed diabetes mellitus type 2 initially treated with oral antidiabetic drugs and later with subcutaneous insulin. He did not experience any bleedings after the subcutaneous injections. Blood pressure was 140/90 mmHg, BMI 33 kg/m^2. His joints had been deteriorating and he suffered from pain and loss of joint function. Between 1987 and 2003 total prosthesis of both his knees and right hip were carried out. In 1990 he started to experience haematomas following subcutaneous injections with insulin.
At examination thrombocytopenia 50 x 109/l was found as a result of liver cirrhosis. Viral examination revealed a chronic hepatitis C infection, genotype 3 and positive anti Hepatitis B surface and core antibodies. Between 2000 and 2003 he had several bleedings from oesophagus varices. Band ligation was performed. In 2004 a Port-à-Cath had to be placed, because peripheral venous access was no longer possible.
In 2005 he was admitted to the hospital because of fever and tenderness and swelling of his right knee. Blood cultures from peripheral blood and also from blood taken from the Port-à-Cath were positive for Staphylococcus epidermidis. A right knee infection was diagnosed and intensive orthopaedic and antibiotic treatment followed. Finely, a new prosthesis could be placed in his right knee and a new Port-à-Cath was placed.
Two months later he developed a Klebsiella pneumoniae sepsis with respiratory insufficiency and he had to be treated at the intensive care department where the Port-à-Cath had to be removed. A liver transplantation has been considered, but because of the complex problems has not been performed yet.

With aging, people with haemophilia may develop diseases previously not seen in this population. These complications might be associated with haemophilia, treatment with clotting concentrates, infections complications or medication. Management of patients born before clotting factors were available is difficult because of a combination of problems. These patients developed haemophilia arthropathy, which limits their mobility and makes orthopaedic operations like joint prosthesis necessary. One of the serious complications of joint prostheses is infection, which requires removal of the prosthesis and a longstanding treatment with antibiotics. Because of poor venous access some patients need a Port-à-Cath, which also increases the risk of bacterial colonisation and infection. The combination of a prosthesis and a Port-à-Cath may therefore be dangerous.

Overweight, diabetes mellitus type 2 and hypertension

Obesitas (Body Mass Index, BMI>30 kg/m^2) is associated with diabetes even in the cohort of mild haemophilia patients.(10) Recommended BMI is <25 kg/m^2 and waist circumference <88 cm in women and <102 cm in men. Weight reduction has a positive effect on the risk factors for cardiovascular diseases as have an increase of HDL-cholesterol, reduction of blood pressure and prevention of diabetes mellitus type 2. Haemophilic arthropathy due to repeated

bleeding into joints results in limited range-of-motion and muscle atrophy. These complications occur mainly in patients with severe and moderate haemophilia and are positively associated with older age and increased BMI.(11)
So due to lack of regular physical activity, haemophilia patients often are overweight, and there is an increased risk for diabetes mellitus 2 and hypertension.(11,12) Regular physical activity decreases the risk for Ischaemic Hart Disease (IHD) directly (13) and indirectly through the reduction of blood pressure and changes of the lipoprotein profile.(14) Lifestyle activities and structured interventional physical activity seem to have a comparable effect on cardio-respiratory fitness and blood pressure. Recent public health recommendations advocate 30 minutes of moderate intensity physical activity per day (15), but for haemophilia patients it is more difficult to design an appropriate training programme and to motivate them to take part. Regular exercises and increase of muscular strength may also be important to diminish the frequency of bleedings and to decrease further joint destruction.(16,17)
Smoking increases the risk of Ischaemic Hart Disease, stroke and aneurysma aortae 2-4 fold in comparison with non-smokers.(18) In 2004 31% of Dutch men and 25% of Dutch women were smoking. In the same year 18 000 persons died due to cardiovascular or lung disease.(19)
Hypertension (blood pressure >140/90 mmHg) increases the risk of death due to Ischaemic Hart Disease, stroke, decompensatio cordis and vascular dementia. The cause of hypertension is mostly idiopathic, but high blood pressure is often associated with nutrition habits and obesitas. Furthermore, stress, physical inactivity, alcohol abuse and smoking have additional negative effects.
Haemophilia is reported to be associated with an increased risk of hypertension but no large control studies have been performed.(10,20)

Case: an acute coronary syndrome

A male born in 1955 was diagnosed to have severe haemophilia B, factor IX <1% B. He suffered from recurrent bleedings and therefore, he started to be treated with the prothrombin complex prophylactically. In 1977 liver functions were disturbed. Hepatitis B serology was negative. Later on, positive hepatitis C serology was found. He was HIV negative. He developed haemophilic arthropathy of the ankles and left knee. In 1994 total knee prosthesis was carried out. In 1999 he was successfully treated with alpha-interferon and ribavirin for hepatitis C and he reached a sustained virological response.
Patient was a smoker since the age of 15; he smoked 20 cigarettes a day. His blood pressure was always normal, but it was not measured on every visit. In 2004 hypertension was diagnosed (160/110 mm Hg) and he was treated with telmisartan (angiotensin II-receptor agonist). BMI was 29 kg/m^2. Kidney function was normal. The total cholesterol was 6.9 mmol/l, HDL cholesterol 0.86 mmol/l and LDL cholesterol 5.22 mmol/l.
His father died at the age of 50 from cerebral infarction. His mother had hypertension. One brother died at the age of 45 years from myocardial infarction.
In 2006 the patient had acute chest pain and an acute coronary syndrome was diagnosed. Bypass surgery was carried out after suppletion with factor IX concentrate given as continuous infusion. No bleeding problems occurred. Treatment with acetylsalicylic acid 80 mg, simvastatine 40 mg, amlodipine (calcium-antagonist) and sotalol (beta-blokker) was started.
The patient is doing well. He gave up smoking. So far bleeding has not complicated this treatment.

Ischaemic heart disease

Data on the protective effect of haemophilia on the occurrence of ischaemic heart disease (IHD) have been conflicting.(2,20-22) In any case, nowadays we often see patients with haemophilia treated by cardiologists and even undergoing invasive coronary surgery. This means that the diagnosis of haemophilia does not preclude the presence of Ischaemic Hart Disease. In the study of Kulkarni, the same risk factors for IHD as those identified for the general population were found i.e. hypertension, hyperlipidemia and diabetes mellitus.(20) Lifestyle factors such as smoking, diet, alcohol and physical activity, together with a positive family history increase the risk of developing of cardiovascular problems.

Liver and kidneys

Chronic liver disease mainly due to hepatitis C and the development of liver cirrhosis make a long lasting and exhausting treatment necessary. The patients often use a combination of pegylated interferon and ribavirin, which might influence liver and kidney function.

Recommendations

Life expectancy of haemophilia patients was found to be significant better among haemophiliacs who receive medical care in specialized haemophilia treatment centres.(24) These centres provide comprehensive specialised care, which is mainly focused on prevention and treatment of bleedings, management of complications of bleedings, and therapy. In addition, psychosocial problems are detected and handled. The management of elderly haemophilia patients includes more than the careful treatment of the bleeding complications. Many older patients with haemophilia may never have consulted their family doctor. Therefore, haemophilia centre staff, mainly the doctors and nurses, should be encouraged to pay attention also to general complaints and signs which are not directly related to haemophilia.

A full patient history including the cardiovascular risks in the family and the use of drugs has to be recorded. Attention should be paid to lifestyle issues like smoking, alcohol, diet, and physical activity. A complete physical examination should be performed including measuring of body weight and blood pressure. Laboratory examination should include kidney function, liver function, sodium, potassium, glucose and routine urine examination. In patients with diabetes, hypertension and a family history positive for cardiovascular complications, cholesterol should be measured as well. Good co-operation with internists and cardiologists is important in the management of these patients.

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Chapter 10. As haemophilia patients are aging ...

R. Bos

Psychosocial consequences of aging

Haemophilia is not just a disorder of young children, adolescents and adults with hepatitis C and HIV infection anymore. The focus on Port-à-Caths, home treatment, arthropathy surgery and interferon treatment is noticeably shifting towards the needs of senior patients. Adequate treatment has improved the life expectancy of haemophilia patients in Western countries. It now nearly equals that of the general population (1) and results in a new category of patients in the haemophilia population: seniors with haemophilia.

Men with haemophilia not only face the challenge of living with premature arthropathy and hepatitis C and/or HIV infection. They are also confronted with the age-related ailments that have been described in the previous chapters. Progressive arthritis and waning strength may result in a need for (more) medical treatment, (more) hospital visits and lead to a loss of independency which causes great concern. Associated with the physical aspects of aging, patients become aware of, or suffer from, psychosocial problems which may be triggered by loss of work, early retirement, loss of health and altered family dynamics. Up till now very little literature has been published about these problems.
Health care providers need to be aware of the aging issues in haemophilia and respond to the needs and requests for help from patients. In doing so, they will optimize haemophilia care and contribute to the quality of life of patients.

Employment and activities

The availability of blood products created the opportunity for patients to take part in society and to enter the labour market. Employment leads to a higher quality of life than being unemployed. Having a job fitting for the patient's education level ranks a good second. Several studies − for instance HIN 5, 2004 − show that haemophilia patients of 15-65 years have increased their participation in the labour market.(2) However, in general haemophilia patients less often have full time jobs and more often suffer from occupational disability than men in general. The differences with the general population are greatest for senior patients.

Generally speaking chronic patients run an increased risk of psychosocial problems. However, chronic disorders are a challenge for the elderly in the third phase of life! For haemophilia patients this is an issue too. With the advancing years many haemophilia patients find it hard to go on working. Their working careers are often shorter than those of other people. Progressive severe arthritis, viral infections and severe tiredness are more of an obstacle than haemophilia itself.
Regular sick leave, medical check-ups and disability interfere with the patients' drive and pleasure in working. Due to the absence of treatment in their youth 75% of the patients >65 years of age have physical restrictions which they label as severe, 20% label them as moderate.(1)
Employers are both legally obliged and willing to adapt working conditions to the restrictions and needs of employees; they provide part-time work, flexible working hours, more fitting

tasks, extra rest periods, and use of ergonomic aids. Nevertheless, to go on working may not always be an option for aging haemophilia patients.
They may have to face involuntary unemployment, changes in social and financial position and loss of social contacts. Coping with these is not always easy. Common themes in the life stories of haemophilia patients are the appreciation of their jobs and how working contributed to their social and psychological well-being. Senior haemophilia patients have never taken their employment for granted. They often feel a strong need to be recognised and accepted as ordinary human beings. This need may drive them to exceed their limits and to go on working for as long as they possibly can.

Case: William (56)

William is a senior patient with haemophilia A and arthropathy in both knees and the left ankle joint. He is married; his two children are living on their own. He worked for ten years as an electrician in a photofinishing laboratory. He had to negotiate several small stairs and walk long distances everyday. Over the years the job became more and more difficult. He was in pain and his strong wish to hold on to the job caused mental stress. In the end increased bleedings and joint problems resulted in frequent periods of sick leave. Finally William was declared unfit for work and sent home. A period of unemployment, uncertainty and psychosocial problems followed. Fortunately the reintegration officer found him a new part-time job as a service engineer for local sport accommodations. William also took up voluntary work at the local platform for disabled persons. William enjoys his new job. His tasks cause less pain and stress. He is optimistic about the future.

Family life

The children leaving home, becoming a grandparent, retirement: these are the major events of the third phase of life. This phase, starting more or less at the age of 50, covers a substantial part of our lives. It is characterized by specific physical and psychosocial issues. Some of these are difficult to deal with, like physical discomfort and pain; others are pleasant: more leisure time and no more pressure to deal with the rat race.
In haemophilia patients (the fear of) bleedings, pain and physical limitations may threaten independence, normal activities of daily and social life. Doing one's share of domestic chores and plans for outdoor activities are never certain. This may lead to a rearrangement of tasks and responsibilities within the family. The consequences may place a burden on family members. Obviously it can be demanding for life partners to find themselves increasingly in the role of caregiver. They are the ones who will have to assist the patient in day to day self care. Those will do best who find an acceptable way to cope with the combination of this 'nursing' role and partner role and maintain equality in their partnership. Keeping an open dialogue is the key!

Besides haemophilia and joint problems the personal and social well-being of the patient is also challenged by transfusion related virus infections. Having chronic hepatitis C or HIV causes psychological distress and places an extra burden on the patient himself and his partner.(3) The possible social stigma, the demanding treatment for chronic hepatitis C and consequences for the patient's relation and sex-life are obvious. Patient and partner have to find ways to cope with their needs and achieve a level of contentment.

Sexuality

'Being old' in itself is no reason for giving up sex. Many seniors stay sexually active in old age, many more, actually, than we generally think. For them sexuality adds to their relationships and their quality of life. Sexuality makes an important contribution to the male or female identity. In addition to self confidence and joy for life 75% of seniors find that sexuality has positive effects on their mental and physical health. People in the third phase of life who enjoy active sex lives and intimate relationships report a higher quality of life.
Some senior haemophilia patients accept that they have to give up sex as a consequence of their joint problems or disability. Other patients want relaxed sexual activities. Unfortunately their sexual capacity is reduced or blocked by pain, fatigue, arthropathy and physical limitations. These haemophilia patients are challenged to find new, comfortable ways to recover their sexual pleasure as a vital aspect of their personal life. Rehabilitative sex therapy offers services and advice on these problems. These are discussed in chapter 11.

Coping strategies[3]

With the advancing years persons with a disease or disability will sooner or later acquire one or more other diseases or disabilities. Just like each phase of life the third phase demands a change in attitude and a general re-orientation on life. Each senior (patient) experiences aging in his own way, depending on gender, personality, one's personal history, social and material position and last but not least one's state of health. Senior haemophilia patients' attitudes to life add an extra dimension to these general items. Some patients never expected to grow old. Looking forward or facing the future was neither discussed nor recommended by health care providers. All of a sudden prophylaxis and home treatment created a brand new perspective and extra lifetime!
Seeking new activities, looking for a new meaning in one's life, an increasing need for care, and looking back on the years gone by, these issues become more important. The senior haemophilia patient's attitude towards life is shaped by the memories from his childhood: long periods in hospital, pain, traumatic experiences, being excluded from school and social activities. Questions like how to live autonomously, how to find a job or a partner created uncertainty. Haemophilia patients often lacked the opportunity to gain social experience. Frequent hospital visits and stays are among their most bitter memories and often interfered with their personal development and plans.

The third phase of life with new freedoms and fewer responsibilities will be enjoyed until limitations caused by disabilities and handicap arise. Increasing disability may interfere with the realisation of plans people made for retirement. Most senior patients want to do volunteer work in the community and enjoy family life like everyone else.

As people grow older, the chance of being faced with the loss of a partner, family members and friends grows. This implies a shrinking of the patient's social network. Although life expectancy in women is higher senior male patients may become widowers and live by themselves for years. Living on your own and loneliness go hand in hand. Increasing loss of health because of progressive arthropathy, liver problems and age-related physical and mental disorders can create an involuntary dependence on care. Living independent lives for as long as possible has always been the clear wish of chronic patients like haemophilia seniors. To

[3] Coping means everything people do to get a sense of control or to recover control in threatening situations or loss.

have to give up an independent life and move into a nursing home can be dramatic for haemophilia patients who have fought for self-determination for so many years.
Going through the aging process with feelings of loneliness, gloom, anger, sadness and a renewed fear of what is ahead can put a strain on one's performance.
How haemophilia patients will cope with these imminent age-related problems has not yet been investigated. Only literature on coping strategies in chronic patients in general is available. Without knowing exactly how people cope psychology tells us that everyone has the skills to accept or to adapt to stressful situations. However, coping with limitations and disability will require outside help. Patients need an accessible network of persons who will offer solid emotional support and practical help during periods of pain, discomfort and uncertainty. Partners and family members are the first circle. Social peer support has also been suggested to act as a mediator or a buffer in coping with illness or stress and promote well-being

Practical needs

Senior patients suffering from physical limitations and disability still wish to live independently for as long as they can. The national social security system and other services can be helpful to realize a self-sufficient life. They provide for special needs in living, sports and transportation. Ergonomic aids are available for walking, climbing stairs, bathing and activities in and round the house.

Case: Peter (72)

Peter is a senior patient with severe haemophilia A and multiple joint problems. Both knee joints have been removed because of regular infections in his prosthesis. His stiff legs only allow him to walk short distances in the house. Being wheelchair bound and single made his life complicated and more dependant on other people. Peter was advised to move to a new comfortable apartment for senior citizens which offered care services. Having lived happily in his small and cosy house in a popular neighbourhood for over thirty years, moving to another part of town was a nightmare. Financial support from the local social security services and others allowed him to carry out extensive adaptations to the house (bathroom, kitchen, toilet, doors). [photo] Two women next door took up his personal and domestic care, financed by the new Personal Budget System of the National Insurance.[1)] Peter is very content that he is able to continue living by himself.

[1)] Since January 1, 2007 there is a new Law in the Netherlands (Wet maatschappelijke ondersteuning) according to which the city councils are responsible for the support of people with a chronic illness or a handicap and the elderly. They are entitled to a Personal Budget to cover the extra expenses related to their health problems.

Healthcare recommendations

All medical and associated psychosocial complications described previously may increase the risk of bleedings in the senior haemophilia population. The complete range of problems is not yet well known and will become clearer in the near future. More research, into psychosocial issues in particular , is needed. It is of great importance that haemophilia health care providers pay extra attention to the physical and mental condition of the aging haemophilia patient. Health care providers should start organizing and coordinating treatment and care for the needs and demands of this group of patients. 'Wellness' programmes including peer meetings

for senior haemophilia patients ought to be instigated. These interventions may help to prevent untoward physical and psychosocial impacts of aging: a challenge to the National Society of Haemophilia Patients.

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Chapter 11. Haemophilia and sexuality

W. Gianotten & L. Heijnen

[photo of bed]

Introduction

There is a confusing relationship between disease and sexuality. On the one hand, many people expect that people who have a disease, have no sex or should not have sex. Accordingly, most health professionals do not raise the subject and neither do the majority of patients and their partners. On the other hand for many people sexuality is such a vital force in their life and in their relationship that they continue trying to find satisfactory sexual expression and intimacy. That is true even for people with a serious disease and physical impairment. Haemophilia, like many other chronic diseases, can be accompanied by sexual dysfunction. In this chapter we will look at sexuality in the aging haemophilia patient, leaving out many of the bio-social and developmental aspects.
For haemophilia care providers sexuality is an important issue since most patients rely on them for all their health problems. And that includes sexuality!

Case: sexuality

Mr X. is a man in his late fifties with severe haemophilia A. He has been married for nearly 30 years. Because of joint problems and functional limitations he has been using a wheelchair since his twenties. Before getting married he has had several girlfriends. "*Being a haemophilia patient was no problem for me and I have had active warm (sexual) relationships*". From the age of 40-45 his right hip caused pain and limitation of motion and when having intercourse he was uncomfortable in the classic missionary position. He and his wife communicate openly and easily and they have been able to find various other positions in which they can caress and make love in a satisfactory way. Examples of positions of comfort are: side-by-side, woman-on-top position or seated in the wheelchair with his wife on his lap. Necking and oral sex are also part of their repertoire.
In addition to the hip problems both his elbow joints deteriorated. Whenever he takes weight on his arms his elbows not only feel uncomfortable but make (disturbing) noises. "*We just put up the music a bit*" he says.
In the 1990's hypertension was diagnosed and a beta-blocker (Atenolol®) was prescribed. Six years ago his hepatitis C was treated with interferon and ribavirin with good result. Since that time he has erectile problems. He and his wife discussed these problems both with his general physician and his haemophilia counsellor. In both cases he had to raise the subject himself but he was happy with the ensuing discussions and support. The couple has a satisfactory sex life because "*fortunately there is much more to sexuality than erections only*".
Looking back he says "*Active sexual counselling should be part of haemophilia care. The haemophilia doctor or social worker/psychologist should bring up this subject as a natural part of the annual check-up*".

Sexual function and dysfunction

Male sexuality is much more than just intercourse and includes among other aspects sexual desire, feeling masculine and being physically intimate. It is a way to relax, to cope with complex emotions, to improve one's self-esteem and as such an important factor in quality of life.
The sexual response usually starts with sexual desire. Desire can be disturbed by many reasons: fatigue, low testosterone (one of the side effects of HAART = highly active antiretroviral therapy), the expectation of pain and as a side effect of antidepressant medication.
The next phase, sexual excitement (physically seen as erection) is very dependent on good blood circulation, proper penile stimulation and no-performance fear. Since aging can go hand in hand with diseases (diabetes, arteriosclerosis and hypertension are the major culprits), senior men more often have erectile problems. In haemophilia an additional factor is (fear for) pain, hypertension and the side effects of antihypertensive and antiviral medication.
For phase three of the sexual response, ejaculation and orgasm, a proper neurotransmitter balance is needed. Here most problems are caused by antidepressant medication.
In the next paragraph we will describe how various aspects of haemophilia physically can interfere with sexuality.

Physical changes

In the acute stage of joint bleeding sexual expression will be marred by pain and sexual desire by the fear of pain. Over the years recurrent bleeding can damage the joints, a situation resembling rheumatoid arthritis (RA). In a group of RA patients 35% thought that their disease strained the relationship with their partner and 56% found that their arthritis placed limitations on sexual intercourse. The principal causes mentioned were fatigue and pain.(1)
RA patients do not differ from controls regarding sexual satisfaction. However, they are less sexually active than controls. And many have problems with their joints during sexual activities.(2) This will be similar for patients with haemophilic arthropathy, especially for those with painful joints and (flexion) contractures in elbows, hips and or knees.

Ilio-psoas muscle bleeding

Bleedings in the ilio-psoas muscle may be a result of sexual activity. They cause pain and functional limitations. Adequate clotting factor replacement and rehabilitation is required to stop bleeding and to prevent long lasting functional limitation and relapse of bleeding. Additional suggestions on sexual behaviour as mentioned in this chapter should be given.

Kidney disease, hypertension and heart disease

The long-term effects of haematuria, common among men with haemophilia, are probably one of the reasons for disturbed renal function.(3) The effects of chronic renal disease on sexuality are (among others) tiredness, low testosterone and high prolactin levels, all decreasing sexual desire.
Another relation with kidney disease is hypertension. Since hypertension in itself damages the circulation, it can cause erectile problems. Usually it is said that hypertension itself is responsible for 9-13% of erectile problems and the various antihypertensive drugs subsequently cause additional damage to both erection and ejaculation.(4)
A man's erectile capacity is so strongly connected to circulatory diseases that nowadays erectile problems are a firm reason to suspect circulatory diseases till excluded. Fortunately,

men with haemophilia still have less than average rates for ischaemic and other types of heart disease.(5) So the risk of erectile problems due to cardiovascular factors is less.

Chronic hepatitis C and HIV

A substantial number of men with haemophilia have been infected with hepatitis C virus and HIV. These infections can influence sexuality in several ways. On the one hand there is the risk and fear of transmitting the virus to the sexual partner. This risk will force most people to use condoms during penetrative sexual contact, and this easily can decrease sexual desire in some patients or partners. On the other hand both the disease itself and the treatment may cause sexual dysfunctions.

Transmission of hepatitis C virus to the partner through sexual contact is very low.(6) In men with chronic HCV infection sexual dysfunction was highly prevalent, independent of depression, and associated with a marked reduction in health related quality of life.(7) In another group with chronic hepatitis C infection, 21% of the men were found to have a sexual dysfunction. The level of gamma glutamyl transpeptidase (GGT) may predict the sexual dysfunction status of patients.(8)
When the HCV positive men are treated with interferon they double their risk to get a sexual dysfunction. They easily develop clinically relevant depression, which is a robust reason for sexual dysfunction.(9) And the combination of interferon and antiviral therapy with ribavirin hampers sexual desire both by a decrease in testosterone which is needed for sexual desire and by an increase in depression.(10)

HIV is more easily transmittable and accordingly can induce more fear with possible effects on sexual desire. In a group of HIV positive men, of which 76% was on HAART, impaired erection was found in 74%.(11) It is not easy to separate the effects of the HIV status and the effects of the HAART treatment. Lamba *et al.* (12) compared HIV infected men with a control group. Low libido and erectile dysfunction were reported in the control group in 2% and 10% respectively. In comparison the prevalence of both problems in HIV infected men not taking HAART is 26%. In men on HAART reduced libido was noted in 48% and erectile dysfunction in 25%.
There seem to be different effects for different antiviral drugs. From data of a retrospective survey it was concluded that protease inhibitors (PIs), especially ritonavir, appeared to increase the risk of sexual dysfunction.(13)

A summary of sexual dysfunctions

What about sexual dysfunctions in the general male population? From a review of 24 studies, Fugl-Meyer *et al.* (14) summarized that erectile dysfunction had a prevalence of 1-9% in men below 40 years of age; in the 40-59 year group it ranged from 2-9% to levels of 20-30%; and in the 60-69 year group a rate of 20-40% was found. Orgasm dysfunction is far less frequent, but the problem of diminished desire is, like erectile problems, increasing with age. In a national USA survey the 50-59 years age group is more than 3 times as likely to experience erectile problems and to report low sexual desire as men aged 18 to 29 years.(15)
The next question concerns sexuality changes in the aging haemophilia population. Above we have shown several reasons for a more than average prevalence of sexual dysfunctions in men with haemophilia. An additional negative psychological influence may be expected since sexuality is strongly influenced by well-being. Moreover, many haemophilia patients suffer from psychological symptoms which may be precipitated by changes in work such as early

retirement and altered family dynamics.(16) However we have no accurate knowledge of sexuality and haemophilia since, up to now, this area has never really been investigated.

What to do?

The most important recommendation for health professionals is: communicate! Since patients are mostly too shy to bring up the subject of sexuality, the haemophilia health professional should proactively do so. First the existence of sexual dysfunctions should be explored. The next step is to find out whether these cause sexual problems. If so information should be given and sexual counselling or therapy offered. The PLISSIT model with different levels of complexity can be used for counselling.(17) PLISSIT stands for Permission (simply offered by proactively talking), Limited Information, Specific Suggestions and Intensive Therapy (for the sexology professional).

In case of haemophilia specific advice should include positions suitable for various joint problems and painkillers before sexual contact. When painful shoulders, elbows or flexion contractures in hips or knees prevent intercourse in the classic missionary position, lying sideways or with the woman on top or in a sitting position can be good alternatives. Erection enhancing methods like the PDE-5 inhibitors (tadalafil, sildenafil or vardenafil) may be useful. However one should be very careful with intracavernous injections. And vacuum therapy is strongly contraindicated in haemophilia since it can cause enormous subcutaneous penile bleeding. Gentle masturbation instead of intercourse is also a good way to adapt to the decreased flexibility or pain of the joints. Depending on the culture suggesting so could be difficult for some professionals, and the method could be unacceptable for some patients. The same applies to the use of a vibrator, which can facilitate both erection and orgasm.

A review with sample strategies for initiating discussion, communicating about sex, and developing goals and interventions can be found in Parish.(17)

The bachelor

Haemophilia can be the reason for not having a partner. However, being single should not be a reason to abstain from sex. When masturbation is morally accepted, it is a healthy way of sexual expression. It can cause emotional and muscle relaxation and has many additional benefits, especially in diminishing the risk of prostate cancer, heart disease and depression.(18) And there are many magazines and (video)films available to make ‘single sex’ more attractive and enjoyable.

Take away message

For professionals:
- Communicate proactively
- If possible, include the partner in information & counselling
- Limit the information given
- Suggest suitable positions and painkillers
- Prescribe erection enhancing medication (tadalafil, sildenafil, vardenafil)
- Refer, if necessary, to a sexology expert

For patients:
- Communicate with your partner
- Communicate with your doctor
- Remember that a sexual relationship is more than just intercourse

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Chapter 12. Aging with haemophilia: Interviews with patients

A. de Knecht-van Eekelen

Introduction

The experiences of older people with haemophilia are not much studied. Just like everyone else they will be confronted with the ailments related to aging. For this book we interviewed a group of people and individuals with severe haemophilia in the age range of 48-71 years old and some of their relatives in order to obtain more information about the day-to-day reality of growing older with haemophilia. Several of the interviewed persons preferred anonymity. That is why we give no names at all. However, we do want to express our gratitude to all for sharing their views on how old age influences quality of life. We hope the narratives will provide health care professionals with a deeper appreciation of the realities of aging with haemophilia.

'The older haemophiliac may take a calculated risk; he will not push his luck.'

General

Among people with haemophilia we find as many differences in attitude towards aging as among the general population. There are men with an optimistic outlook and there are men who worry a lot. There are men with a family around them and there are men who live on their own. Some men socialize easily, others are more retiring. Some suffer more than others from age-related illnesses: diabetes, heart and coronary diseases, osteoporosis, etc. Expectations of what old age will have in store for them will vary with their physical and psychological conditions, their characters and their social situations. However, there is at least one thing all older haemophiliacs have in common: there was no proper treatment for haemophilia when they were young. This means they share similar experiences in the past: depending on the severity of their haemophilia they had regular bleedings, some had to be hospitalized frequently and were immobilized in plaster casts, some may have acquired inhibitors, some have been infected with HIV, many of them have been infected with HCV. Due to untreated bleedings in the past, their joints have been ruined giving them increasing troubles when growing older; they all have to deal with that. Progressive arthritis and waning strength may lead to loss of independence, which causes great concern.

I realize that I am getting older. It seems as if this body keeps breaking down on me. But as long as I am sound of mind, I won't complain. Because even with arthritis and heart disease, I can still do a lot of things and have a lot of joy in life. When I was younger, I would have felt sorry for someone like me. Now I feel very fortunate. I am grateful for my life.(1)

This must be a quote from someone with an optimistic character. Among the persons we interviewed some shared this feeling, others worried, and felt increasingly lonely and handicapped. Those with an optimistic outlook told us that one should experience old age as 'a blessing', and turn it into something good. Seen from the 1950s perspective of a life

expectancy of barely 20 years, it is indeed a miracle that so many severe haemophiliacs are in their sixties and seventies now.

Support systems are in place. Partner/spouse often is a key component of managing the disease and preventing complications on an everyday basis. The death or absence of a family caregiver can present considerable challenges.(1)

Family and relations

In the past it was not easy for boys with severe haemophilia to lead normal lives. Long periods of absence from school, not being able to take part in sport activities, no dancing at school balls, there were many restrictions. And if they disregarded their haemophilia and overreached themselves, a bleeding could be the result. Some found girlfriends and married, others did not. Some interviewees recounted how their relationships started. Several told me that as soon as the girl's parents understood that the boyfriend had haemophilia they tried to persuade their daughter to leave him. These parents could have known that these warnings invariably have the opposite effect. For the young and in love all future problems disappear behind a rosy horizon. One of them remembered telling his love "I do not fit into your carefree world", but she did not want to worry then and she still does not care for doom scenarios now.

As an outsider one admires the way in which all these people take their situation for granted. Of course they went through hectic events, especially before the seventies when no proper treatment was available, praying they would not have bleedings, having to postpone outings, even holidays, because of bleedings. But they are very realistic and adapt to their changing perspectives.

Some of the men we spoke have children. Having a father with haemophilia does not worry children. Children are flexible and accept their father the way he is, because he is the father they know. When they grow older they become more aware of his situation, but they are not really that concerned. When he speaks of his gruesome past they will tease him: "Here come the grandfather's tales again". Asked about their children the interviewees mention their worries about their daughters being carriers. But they never considered abortion: "You do not abort a healthy baby".

Some of our interviewees are grandfathers. One of them says that fortunately none of his grandchildren have haemophilia. He supposes his daughter would have chosen termination had the unborn grandson been diagnosed with haemophilia. However the daughter of one of the other men we spoke has a 4-year old son with haemophilia.

The grandfather remembers the delivery and how negligent the specialists were. His experience underlines the general feeling that those who are not familiar with haemophilia tend to underestimate the risks. It should be common knowledge that carriers may have decreased clotting factor levels and that their sons have a 50% chance of having haemophilia But in this case, which happened only a couple of years ago, neither the obstetrician, nor the paediatrician or nurses acted accordingly. His daughter did not receive adequate replacement therapy, they did not monitor the baby properly and even dropped him after delivery.

After many problems they decided to visit the Van Creveldkliniek (VCK). Here they found a reception which was completely different from other hospitals. They specially appreciate the way the team cooperates. And the grandfather knows the difference; he has a long haemophilia history, with a grand total of 44 hospital stays in the years before his marriage. How does he deal with his grandson having haemophilia? This is not easy for him. "He is over anxious", says his wife, and he admits being nervous when he sees his grandson take a

fall. Of course he knows that with prophylaxis the risk of a bleeding is limited, but even so … And the 4-year old grandson provokes him of course, that is what children do.

> **‘You can achieve if what you really want.’**

Work and retirement

People in the Netherlands mostly retire at the age of 65. At 65 every person in the Netherlands receives old age benefits (AOW) and employees often receive an additional pension. Entrepreneurs can continue to work for as long as they want or need to.
Many haemophiliacs take an active part in society. Their daily life is not much different from that of other people. Some take on voluntary work, manage the household and take care of their families; others have paid jobs generally in the field of administration, finance, consultancy etc. Being in regular daily contact with other people provides an important fulfilment of their daily life. With the advancing years these daily activities will change especially after retirement. Obviously this is a major change in one’s life, for everyone, and perhaps even more so for older haemophiliacs because they have had to fight so hard to achieve their social positions. Older people with severe haemophilia never regarded being employed as a matter of course. Many were so determined to work and live normal lives that they did better than the average employee. Having held a regular job for over forty years, hardly ever skipping a days work, these are achievements haemophiliacs are really proud of.
One of the interviewees, who had worked till the age of 65 despite severe arthropathy and functional limitations, would have preferred to continue in the job, but because 65 was the legal retirement age, that was not allowed. He misses the daily activity, the responsibility and the contacts with other people.
Another man, however, experiences more physical problems. In his fifties he has decided to reduce his working week to three days. By doing so he expects to be able to go on working until the age of 65.

> **‘Your physical and psychological resilience decrease when you grow older; you have been fighting for so many years.’**

Housing

In the Netherlands social security and other insurances pay for adaptations in private houses. With the proper indication one has the opportunity to live in houses built for people with special needs. These are either bungalow type houses or service apartments, often in or adjoining a larger care facility. The extent of care depends on the individual needs. Haemophilia patients are entitled to such care if and when they become handicapped.
One of the interviewees and his wife have decided to move to a facility better adapted to his increasing loss of mobility. He has problems walking the stairs and wants to live on the ground floor which is also accessible by wheel chair. That is the main problem when getting older, “one has to accept a gradual reduction of one’s powers”. He has more and more symptoms from chronic joint damage; especially standing for longer periods has become impossible.
Other people, however, prefer to stay in their familiar homes and environment. Provided the right adaptations are made in the house, being able to stay in the neighbourhood where you have lived for fifty years or more has many advantages. Everybody knows who you are; your family often lives close by; your neighbours will help out. And in particular when you live on your own, you have to be able to depend on your old social network.

One of the issues that worries some of the older men is how to deal with a possible admission to a nursing-home where employees know nothing about haemophilia care. How will they survive in such an environment? Would training of nursing-home staff be an option? That has to be doubted as the number of patients will be very small compared to the total group of people spending their last years in a nursing-home.

‘Act when you feel good, do not postpone whatever you want to do.’

Mobility

The men we spoke pointed out that they all have learned to live with constraints from their youths onwards. This implies that they are used to setting goals that are within their reach. They are also used to the disappointment of not being able to take part in activities because of a bleeding. Some never went on holiday; others chose holiday destinations close to well-equipped hospitals; and if they decided to go caravanning (a favourite Dutch holiday) they would make sure they could rely on the assistance of the Dutch Automobile Club (ANWB) in case of emergencies.

To get around some used a bicycle for as long as they could. With special adjustments a bicycle can continue to be an important added option of mobility. And cycling keeps you fit and in shape. However, most men with haemophilia (have to) drive a car to get around. To obtain and keep a driving licence a special medical examination may be necessary. In the past cars were provided as mobility aids through a social security programme. Nowadays one can only receive extra benefits if one is dependent on a car to get around. There is a wide range of useful adaptations for cars. [photo of car]

It is interesting to note that some haemophiliacs do not want to apply for special benefits, even if they are entitled to them. Or to apply for a parking permit allowing them to park in places reserved for the handicapped. For them it is important to be like everyone else and not a person with special needs.

This generation feels that for today’s young boys with severe haemophilia life is totally different. These young ones have a completely different youth with prophylaxis with safe clotting factor concentrates at hand. The physical condition of today’s young haemophiliacs is so much better, ‘they can do whatever they like’.

‘I learned to be my own mediator.’

Treatment and doctors

In the seventies of the 20th century most Dutch people with severe haemophilia were able to choose for home treatment. Using prophylaxis made them rather independent from the hospital. With the information from the Dutch Haemophilia Patient Society (NVHP), the specialists in the haemophilia centres and contacts with fellow patients these spokesmen accumulated extensive expert knowledge of haemophilia. Over the years they gained quite some experience and developed a special awareness of their own body, while physicians gained little or no experience of haemophilia. Many older men with haemophilia may never have consulted a general practitioner (GP) because of the rarity and complexity of their disorder. In general they would visit the specialised haemophilia centre several times a year consulting with their treater. But when the haemophiliac contracts a disease, then he needs a doctor, another specialist.

There isn't a network; there just seems to be one specialist who seems to only consider one aspect of the whole. I sometimes feel that you (health care practitioners) are building or putting together a puzzle without the picture.(1)

The experiences of our interviewees with other doctors than their haemophilia treater vary. It is obvious that there are GPs and specialists who can not deal with an emancipated, eloquent, well-informed haemophiliac. In those cases the haemophiliac tries to contact his treater at the earliest opportunity. In fact this is one of the major fears: not being able to explain to a physician or nurse or any other health care professional that the haemophilia centre should be contacted immediately and that proper clotting factor correction might be vital. What to do when you fall or have an accident, and lose consciousness? Wear a medical alert locket on a chain around your neck? The men we spoke are not convinced that this will help. In their opinion the relation between patient and physician is changing. In larger cities GPs keep office hours and outside these hours patients have to contact a central primary care emergency post. The experience with haemophilia of the medical staff there is very limited, and it is often difficult to get proper care. In the past one's GP used to be available at all times.
The men agree on the need for a specialised comprehensive care haemophilia centre like the Van Creveldkliniek. They would like to see their haemophilia treaters in a key role mediating between them and other health care professionals.

'Orthopaedic surgery should improve the next decades of my life.'

Orthopaedic surgery

For many senior haemophilia patients the time will come when they have to decide on orthopaedic surgery. Increasing pain in one or more joints can make life unbearable. However, an operation is not without risk, and the results remain uncertain. From our discussions it transpired that people tend to postpone surgery for as long as they can. In retrospect one of the men admitted that before surgery his capacities had been gradually deteriorating. Because this was a very gradual process he long accepted his increasing immobility. However, finally the time had come that the pain grew unbearable and he became a burden to his family and himself. In the absence of pain orthopaedic surgery is not an option. Even extensive loss of motion is generally no motive for surgery as long as daily activities can be managed without pain.
The decision to go for orthopaedic surgery was generally taken after long periods of pain and diminishing quality of life. Anxiety about possible complications ran high, but the expected results tipped the balance. Indeed, complications did occur in some cases and results were not always according to expectations. However, the men we spoke agreed that without surgery they would be in worse shape. "You lose some, but you also gain some", was their view.
In retrospect they realize they should not have waited that long before deciding on surgery. Long periods of pain should be reduced as in the end an operation will be inevitable. Clearly this is not an easy decision. Treaters who recognize their patients ambivalence ought to support the decision process by providing all necessary information.

'People are inundated with information, but they do not take it in until they really need to know.'

Viral infections

The medical issues related to infection with HIV and HCV are discussed in chapters 4 and 5. In 1985 16% of Dutch haemophilia patients were infected with HIV. Nowadays people with haemophilia and HIV can be treated adequately with HAART combination therapy. HIV positive haemophiliacs have lived with a positive diagnosis for several decades now. However, as Smit writes in chapter 2, haemophilia as a disease faded into the background and the consequences of his HIV infection took up centre stage. The most imminent threat is the long-term effect of the daily intake of HIV inhibiting drugs and the overall development of the infection.

Almost all older patients with severe haemophilia have been infected with hepatitis C (HCV). In 80% of them this has resulted in a chronic infection. Since 1990 therapy for chronic HCV infection is growing more effective, but side effects of treatment with interferon and ribavirin are common. The real problem is that HCV infection is asymptomatic in the first stages and it may be many years before End Stage Liver Disease develops, if at all. Obviously patients may be reluctant to start treatment and need to be convinced that treatment really is indicated. One of the men we spoke was rather sceptical about treatment for HCV. He thinks HCV is a hype and doctors tend to use patients as guinea pigs. In his opinion there is a discrepancy between the flood of information on possible risks of HCV and actual chance of acquiring End Stage Liver Disease for him as an individual. But even he was persuaded to start therapy for HCV. “You feel compelled to co-operate, out of obligation to your kinsfolk as well”. Chapter 5 describes the side effects of HCV treatment: ‘Psychological problems like irritability and concentration problems occur in more than 80% of patients and depression requiring antidepressant drugs in one fifth of patients’. But what does that mean to the man who is that patient? In this case he could not cope with the negative effects of the medication. He felt like another person, so tired, depressed and ill that he decided to quit the programme. The price was too high for something he did not perceive as life threatening.
Would that be typical for older patients with severe haemophilia? Have they gone through so many critical emergencies, in which their lives may have been at stake that they do not want to worry about eventualities in a distant future? Evidently in such a situation the relationship between a patient and his health care providers is very important. Building such a relationship takes mutual respect and open two-way communication to ensure the best fit between the doctor’s recommendations for treatment and the patient’s preferences. The patient needs to be seen by a specialist who has a good understanding of HCV, its diagnosis and treatment, but also has affinity with persons with chronic diseases.

In conclusion

For the generation of people with haemophilia born before 1960 growing older means a multiplication of contacts with all kind of specialists. This is what concerns them most. They prefer a comprehensive approach and put quality of life first and foremost. In a comprehensive care centre like the Van Creveldkliniek-haematology they receive well coordinated care. All the men we spoke value well coordinated care. For some of them it was a reason to change hospitals. It is essential that the treater coordinates care to prevent patients loosing their balance in the turns of the medical merry-go-round.

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Chapter 13. Perspectives and practical advices

E.P. Mauser Bunschoten, C. Smit & A. de Knecht-van Eekelen

An aging society

The aging of the world population is creating new perspectives. At economical level, a long life is connected with evident socio-economical problems. Life after retirement may count several decades. And while some needs are more connected with the life of younger adults and become less relevant for the elderly, others grow rapidly.
Residual functional capacities are reduced and extended medical support is necessary. In the Netherlands the aging population requires an extensive health care programme. Coping with chronic degenerative diseases accumulating over the years is one of the major issues.
Co-morbidity is quite common in the latter phases of human life. In their everyday practice with elderly patients most clinicians are confronted with co-morbid diseases, while conceptual and scientific evidence on these issues is lagging. There are important conceptual linkages between co-morbidity and other processes in elderly populations, such as disablement and frailty. To very basic questions there are currently no clear answers. How is co-morbidity related to aging? Are there ways to prevent or reduce co-morbidity? There is little or no clinical and scientific research on how to organize the complex treatment for these old people. Little is known about the best ways to provide practical and medical care. The Dutch Council for Health Research [Raad voor Gezondheidsonderzoek] is recommending to focus research on three main topics: co-morbidity problems, practical guidelines, and organisation of care.(1)

Given the current and projected growth of those in the older age groups new and emerging care technologies are targeted at supporting the care needs of these older people within the domestic environment. A spectrum of care technologies exists or is being developed to address these needs. These developments look promising for older haemophilia patients as they might add to their quality of life. Existing research indicates that older people very often delay seeking care support, preferring to ‘soldier on’ with pain or discomfort, accepting that these are part of their everyday life. However, if new care technologies monitor and report on their physical condition this may produce new anxieties and stresses for a wide range of workers and patients.
But new technologies need to take seriously older people’s ongoing and ever-changing needs for meaningful human interactions. Older people – and the same can be said about older haemophilia patients – do not want to be ‘stuck’ with a narrow range of others, but to maintain a diverse and extensive social network. They also desire reciprocity in social interactions. Meeting these social needs is central to older people’s health status – people cannot be well unless they have meaningful and satisfying social networks.(2)

Healthy aging

Aging and especially ‘healthy aging’ is on the political agenda. Co-funded by the European Commission, a three-year (2004-2007) ‘Healthy Ageing’ project aims to promote healthy living among people of 50 years and over.(3) One of the main aims of the project is to produce recommendations and policies/strategies for senior citizens health. Health promotion for the aging European population is an urgent and essential task. It focuses on transecting

socio-economic determinants valid for all themes, inequalities in health, gender, and minorities.
In the European Programme there are ten topics to be studied:

1. retirement and period before retirement,
2. social capital,
3. mental health,
4. environment,
5. nutrition,
6. physical activity,
7. injury prevention,
8. substance use/misuse,
9. use of medication and associated problems,
10. preventive health services.

In the Netherlands the government has launched a scientific programme, the 'Programme Growing old successfully' [ZonMw Programma Succesvol Ouder Worden], to stimulate research on aging issues in the Netherlands. The Programme has recently been evaluated. It appears that an increasing number of studies, especially multidisciplinary studies – will be published. Some of the issues that are covered are: cognitive aging, easy-care assessment and prevention of falls.

What is the significance of all this for senior haemophilia patients? In the previous chapters we discussed aspects of co-morbidity, retirement and early retirement. The views expressed in this book are in line with the guidelines of the European Union that mention 'prevent illness in the workplace, promote healthy lifestyles and a supportive and stress-free transition from work to retirement'.
Topic 6, physical activity, is of special interest to patients with haemophilia. It states:

'Increase the level of physical activity for the elderly in order to reach the international recommendations of 30 or more minutes of at least moderately intense physical activity on most, preferably all, days of the week'.

This means that physical functions in haemophiliacs must be such that physical activity is practicable. Physical therapy, rehabilitation and ultimately orthopaedic surgery are ways to reach this goal. It is the role of the comprehensive care team of the Haemophilia Treatment Centre to initiate and coordinate this aspect of care.

However, for those who are involved in haemophilia care, topic 9 'Medication and associated problems' may be even more interesting as it states:

'Problems associated with the use of medications may be avoided by the systematic use of quality indicators for drug use and better co-ordination among care providers. Surveys of therapies and the inclusion of older people in clinical trials will also be of use'

According to this statement we can opt for a new role for haemophilia treatment centres.

A new role for haemophilia treatment centres

In a model of integrated, holistic care, new forms of care may be developed and new infrastructures for cooperation set up. Here – in our opinion – is an important role for the haemophilia treatment centres (HC). In the new setting a HC should take responsibility for the

coordination of care. Such a setting would also be much more capable of addressing compliance issues. The haemophilia nurse or nurse practitioner could spend more time giving instruction and guidance to patients, which eventually will result in better compliance. They should instruct patients to always contact the HC in case of medical diagnostics, interventions and surgery. Patients should also be aware that they themselves are the key persons in realizing good coordination of care by the HC.
In this phase of life senior patients once again need support and recognition. In their past, busy working lives they literally did not have much time for their peers' experiences. But now, retired and having to learn to cope with co-morbidity and old age problems, they once again like to exchange ideas with their peers. They may discuss day to day activities and events as well as medical issues. Sharing physical exercise together – f.e. training in the pool – and other group activities will boost the patient's powers. The HC – sometimes in conjunction with the patients association – can organize these group activities. Joint medical consults organised by the HC can also offer the opportunity to learn from each others ups and downs.
National haemophilia societies could also play an important role in pushing the issue of aging way up on the political agenda. This new responsibility promotes the interests of – most likely – lifelong members who will be the first to benefit from new and innovative approaches.

SWOT analysis

One of the tools that could be realised by haemophilia centres, is a SWOT (strengths, weaknesses, opportunities and threats) analysis for older patients or for those who want to be involved in such an exercise. The SWOT should be applied to analyse the weak and strong points in daily life.
For example, living on one's own on the second floor of an apartment building that has no elevator, can be marked as a possible weak point. In contrast, an apartment with no stairs counts as a strong point, because a haemophilia patient can go on living there when advancing in years. Having a partner who can take assist in home-treatment and so on, is another strong point. A SWOT analysis may help the person, who is living on the second floor, to see it would be wise to avail himself of the opportunity to move to an apartment for seniors with easy access and the availability of various services like a community restaurant, a health care centre etc.
For a patient not on home-treatment travelling to a hospital may cause problems when he is growing older. That is a weak point. This travelling could be replaced by care of a district-nurse who will transfuse clotting factor in case of an emergency or on a prophylactic basis.
Of course, this type of SWOT-analysis is not restricted to older haemophiliacs, it can be used by all age groups. It certainly can be a good tool for haemophiliacs or haemophilia treatment centres to analyse and solve future problems of elderly haemophiliacs.

Anticipatory guidance is needed. This means programming for education and support to assist people with haemophilia and their families; programmes to prepare for and deal with transitions they will experience. Creative strategies for integrated management of multi-morbidity should be developed. We recommend that people with haemophilia be involved in the planning and development of programmes and strategies to address the needs of elderly people with haemophilia.(4)

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Recommendations in this book

Chapter 1. Life expectancy and co-morbidity

The haemophilia treater should be the key person in the co-ordination of care in order to guarantee the best level of care. Good co-ordination and education of patients and health care professionals may prevent complications.

Chapter 2. Coping with disability and co-morbidity: a patient's perspective

How to avoid complications? Stay in regular – at least once or twice a year – contact with medical or nursing staff of your haemophilia centre even when there may be no acute medical reason. Inform any physician that you have haemophilia and that your haemophilia treater should always be contacted to discuss the treatment regimen. Call your specialist yourself and check if care is co-ordinated. Instruct your partner or family members to inform your haemophilia treater when you are hospitalized in another hospital in case of emergency hospitalization or traffic accident.

Chapter 3. Haemophilic arthropathy: Rehabilitation and orthopaedic surgery

Fall prevention
The most effective fall prevention strategies are multi-factorial interventions targeting identified risk factors, exercises for muscle strengthening combined with balance training, and withdrawal of psychotropic medication. Home hazard assessment and modification by a health professional is also helpful.

Joint replacement
Joint replacement therapy can improve activities, participation and quality of life of elderly patients with painful arthropathic joints.

Pain Schedule
1. Paracetamol is the initial medication of choice; if not effective
2. Paracetamol and codeine (10-20 mg max 6 times a day)
3. For severe pain paracetamol and a muscle relaxant
4. For very severe pain morphine (MS Contin®)

Other measures:
1. Distal traction
2. TENS
3. hot packs

Chapter 4. HIV in haemophilia

Younger age at seroconversion appeared to be one of the most important factors associated with improved survival before the introduction of HAART.

Increased bleeding tendency due to HIV protease inhibitors has been reported in 15% of patients. Bleedings may be unusual because of their atypical location in soft tissues or muscles, or bleeding frequency may be higher than usual.

Chapter 5: Treatment for Hepatitis C

Follow up of patients with HCV
Patients with haemophilia and chronic hepatitis C must be checked regularly.

Follow up	ALT, gamma GT, thrombocyte count	Prothrombin time, alfa foeto-protein	Transient elastography	Ultrasound
frequency	2 x year	1 x year	once in 2 years	once in 3 years

HCV therapy
Currently the state-of-the-art treatment for HCV consists of pegylated interferon (PegIFN) once a week and ribavirin 800-1200 mg daily.

Chapter 6. Inhibitor development

A haemophilia consultant should always be aware of the risk of inhibitor development in an elderly patient with mild haemophilia. These patients may pose an additional problem because limited information is available on the treatment of this specific patient group. Treatment with bypassing agents or DDAVP can be instituted.

Chapter 7. Prevention of cardiac diseases

Prevention of atherosclerosis by diminishing risk factors such as smoking, hypertension, hyperlipidemia, diabetes and obesity in the haemophilia population is mandatory. Physical activity is important to reduce these risk factors.

Data are needed on the risk/benefit of secondary prevention with anti-platelet agents in this vulnerable population.

Chapter 8. Invasive diagnostics and surgical interventions

Mobilization
Pain and functional limitations due to arthropathy often increase when patients are immobilized after surgery. Early mobilization is the most important intervention. If this is not possible, the help from an experienced physical therapist is needed to prevent further disability.

Thrombosis prophylaxis during complete clotting factor correction
Use elastical stockings preoperatively and until the patient is fully mobilised.

In addition, consider low molecular weight heparin (LMWH) for thrombosis prophylaxis. LMWH is started after complete clotting factor correction or postoperatively, if haemostasis is secured and continued for the period that factor levels are aimed >50%.

Chapter 9. Internal disease

As life expectancy of haemophilia patients was found to be significant better among haemophiliacs who receive medical care in specialized haemophilia treatment centres patients should be treated in such a centre.
The management of elderly haemophilia patients includes more than the careful treatment of the bleeding complications.
A full patient history including the cardiovascular risks in the family and the use of drugs has to be recorded. Good co-operation with internists and cardiologists is important in the management of these patients.

Items for yearly check-up for the aging haemophilia patient

Physical examination	Laboratory test	Urine test
blood pressure body weight	glucose; Ur, Creat; Na, K; γGT, ALAT cholesterol	glucose protein

Chapter 10. Psychosocial consequences of aging

It is of great importance that haemophilia health care providers pay extra attention to the physical and mental condition of the aging haemophilia patient.
'Wellness' programmes including peer meetings for senior haemophilia patients ought to be instigated. These interventions may help to prevent untoward physical and psychosocial impacts of aging.

Chapter 11. Sexuality

Take away message

For professionals:
- Communicate proactively
- If possible, include the partner in information & counselling
- Limit the information given
- Suggest suitable positions and painkillers
- Prescribe erection enhancing medication (tadalafil, sildenafil, vardenafil)
- Refer, if necessary, to a sexology expert

For patients:
- Communicate with your partner
- Communicate with your doctor
- Remember that a sexual relationship is more than just intercourse

Chapter 12. Views from patients

For patients growing older means a multiplication of contacts with all kind of specialists. They prefer a comprehensive approach and put quality of life first and foremost. In a comprehensive care centre they receive well coordinated care.

Chapter 13. Perspectives

A haemophilia treatment centre (HC) should take responsibility for the coordination of care. and address compliance issues. The haemophilia nurse or nurse practitioner should give instruction and guidance to patients, which eventually will result in better compliance. They should instruct patients to always contact the HC in case of medical diagnostics, interventions and surgery. Patients should also be aware that they themselves are the key persons in realizing good coordination of care by the HC.

About the Authors

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Ruud Bos studied Social Work and Services at the Academy of Social Sciences in Den Bosch and graduated in 1994 with a bachelor's degree. He has been employed as a medical social worker at the Van Creveldkliniek, department of haematology, University Medical Centre Utrecht, the Netherlands since 1999. As a member of the multidisciplinary team he has been providing care and education for well over 8 years. His experience includes severe and moderate haemophilia patients, haemophilia families, VWD patients, with or without arthropathy and co-infections. His special expertise is patients on interferon treatment. He is responsible for providing long and short term psychosocial counselling, casework services to patients and families and meeting practical requests for help. Setting up sport camps for different age groups and organising peer meetings for families with young children are also part of his job.
Ruud Bos is a member of the WFH Psycho Social Committee.

Ende, M.E. van der

Ineke van der Ende studied medicine at the University of Leiden and after graduation specialised in internal medicine and medical oncology. At present she is working as an internal medicine specialist at the department of infectious diseases of the Erasmus Medical Centre of Rotterdam University. She has specialized in the care of HIV patients. In 2000 she received her PhD on the thesis titled *HIV-2 pathogenesis and antiretroviral therapy*. She is the author of over a hundred publications, mainly on HIV.

Gianotten, W.

Woet L. Gianotten studied medicine in the Netherlands and graduated in Utrecht in 1967. He started his career practicing tropical medicine for 5½ years in West- and East-Africa. After that he specialised in gynaecology and obstetrics and then in sexology. He enrolled in postgraduate psychotherapy training in order to better address the emotional aspects of sexual problems.
Over the past 30 years, his professional focus gradually shifted from male-female differences and sexual abuse to the sexual consequences of various physical conditions. He has a special interest in reproduction, chronic disease, physical rehabilitation and cancer. Until his retirement in 2006 he worked at the Centre for Reproduction of the Erasmus MC in Rotterdam and was a senior lecturer in Medical Sexology at the University Medical Centre Utrecht. He is a consultant in physical rehabilitation sexology and still practices rehabilitation sexology in De Trappenberg, a rehabilitation centre in Huizen (the Netherlands).
Woet Gianotten is co-founder of the 'International Society for Sexuality and Cancer' and co-editor of the Dutch-Flemish textbooks *Sexology* and *Handbook of Sexuality in disease and physical impairment*.

Grønhaug, S.

Ms Siri Gronhaug acquired her nursing licence in 1977 and has over 25 years of experience caring for both children and adults. Ms Grønhaug is now a registered nurse at the Centre for Rare Disorders at the National Hospital in Oslo, Norway. She previously held staff and

freelance nurse positions in the intensive care units of the Ullevål University Hospital and various nursing facilities in Oslo.
Ms Grønhaug's work at the Centre for Rare Disorders involves extensive travel in Norway in order to facilitate the coordination of community outreach support and home treatment programs.

Heijnen, L.

Dr. Lily Heijnen first encounter with persons with haemophilia was during her internship in the Van Creveldkliniek, the Dutch National Haemophilia Centre, in 1972. After graduation in 1973 she worked there for 6 years as a general physician, before specialising in physical medicine and rehabilitation (PM&R).
In 1983 she qualified and became and still is consultant in PM&R in the Van Creveldkliniek, nowadays part of the department of haematology, University Medical Centre Utrecht. In 1986 she received her PhD on the thesis titled *Haemophilic Arthropathy. A study of the joint status of haemophilic patients comparing prophylactic replacement therapy with treatment on demand*.
She participated in workshops in India, Pakistan and China with the aim to train the trainers, educate patients and their families and convince everybody that physical activities are a must with the motto "Use it or Lose it". Currently there is a co-operation and twinning between the Lahore Hemophilia Patients Welfare Society (HPWS) centre and the Van Creveldkliniek. One of the results was the book: *Comprehensive Haemophilia Care in developing countries*, with emphasis on musculoskeletal aspects.
At present she is member of the board of directors of the combined rehabilitation centre De Trappenberg and the lung rehabilitation centre Heideheuvel and the Dutch Asthma centre Davos, Switzerland.
In addition to haemophilia she has specialised in the rehabilitation of people with cerebrovascular accidents and is vice president of the Dutch CVA working party.

Kleijn, P. de

Piet de Kleijn studied physical therapy at the Academy of Physical Therapy in Utrecht and graduated in 1979. Since 1980 he has been involved in haemophilia care, since 1988 he is responsible for physiotherapy care in the Van Creveldkliniek, department of haematology, University Medical Centre Utrecht. He is the author of 4 articles in *Haemophilia* and co-author of 13 more. He has written several chapters in haemophilia related books. He was a member of the Musculoskeletal Board, advisory board of the World Federation of Haemophilia, from 2000 till 2006. For the World Federation of Haemophilia he has led many workshops and training programmes in India, Malaysia and Pakistan. He is now involved in a twinning programme with the haemophilia chapter in Lahore, Pakistan and in implementing basic physiotherapy in haemophilia centres in Egypt, starting with a pilot project in Cairo in November 2007.

Knecht-Van Eekelen, A. de

Annemarie de Knecht-van Eekelen studied biology in the University of Utrecht. In 1984 she received a doctorate in history of medicine on her thesis *Towards a rational infant feeding. The science of nutrition and paediatrics in the Netherlands 1840-1914*. From 1991-1998 she taught history of medicine at the Free University of Amsterdam. In 1998 she published *Hemofilie, een ziekte in beweging* [Haemophilia, a disease on the move] a history of the Van Creveldkliniek. With Eveline Mauser-Bunschoten and Cees Smit she edited *Rare Bleedings*,

the previous volume in this series. Until 2007 she managed the international consultancy and training activities of Cito, Institute for Educational Measurement in Arnhem, the Netherlands. She has written over a hundred articles and several books on the history of nutrition, hygiene and other subjects in medical history.

Knegt, R.J. de

Rob de Knegt studied medicine at the Erasmus University Rotterdam. After graduation in 1987, he did research into the pathogenesis of hepatic encephalopathy which resulted in a thesis in 1993. Meanwhile he had started his clinical training in The Hague and Leiden. On registration as an internist in 1996, he specialised in gastroenterology at the University Hospital Groningen. He was a member of the Groningen Gastroenterology-staff until 2003 with a special interest in hepatology and liver transplantation. In 2003 he transferred to the Erasmus MC in Rotterdam. He is now one of the Dutch opinion leaders in the field of hepatitis C. After a period in the Hannover Medical School in Hannover, he introduced abdominal sonography for gastroenterologists in the Netherlands. Currently he is involved in the treatment of liver and liver-transplant patients. In addition he is leading and participating in different research projects on hepatitis C, non-invasive measurement of liver damage, and abdominal sonography. He is a member of the Dutch Society for the Study of the Liver, and Chair of the Pharmaco-Therapeutic Committee of the Dutch Board of Gastroenterologists. He is a regular teacher in abdominal sonography for the Chamber of Physicians of Lower-Saxony, Germany.

Leebeek, F.W.G.

Frank Leebeek studied medicine at the Erasmus University in Rotterdam and graduated in 1990. During his medical studies he worked for 4 years as a research fellow at the Gaubius Institute in Leiden and the department of Internal Medicine at the Erasmus Medical Centre Rotterdam. He received his PhD on the thesis *Clinical studies in fibrinolysis inhibitors synthesized by the liver* in 1990. He worked for two years as a postdoctoral fellow at the department of Pathology of the University of North Carolina at Chapel Hill, studying the regulation of fibrinogen synthesis by interleukin-6. He subsequently worked as a resident in Internal Medicine (board certified in 1997), followed by a fellowship in Haematology (board certified in 1999) and was board certified as a vascular medicine specialist in 2005. At present he is working as a haematologist with a main interest in haemostasis and thrombosis at the Department of Haematology at the Erasmus University Medical Centre Rotterdam, the Netherlands. His research interests include the role of various coagulation factors in the pathogenesis of arterial thrombosis and optimizing diagnosis and treatment of bleeding disorders. He has been a (co-)author of more than 80 articles and chapters in books on haemostasis and thrombosis. For his research on arterial thrombosis he received a ZonMw Clinical Fellowship in 2003. He is currently chairman of the Dutch Haemophilia Treaters Society.

Mauser-Bunschoten, E.P.

Eveline Mauser-Bunschoten studied medicine at the University of Groningen and graduated in 1978. Since 1979 she has been working at the Van Creveldkliniek, department of haematology, University Medical Centre Utrecht. In this haemophilia centre over 800 persons

with haemophilia and related bleeding disorders are treated. In 1995 she received her PhD at the University of Utrecht on her thesis *Complications of haemophilia care*.
She has participated in many clinical trials and research projects and is the (co-)author of over 80 publications on haemophilia. Her special field of interest is hepatitis C infected haemophilia patients and bleeding tendency in carriers. She is involved in a twinning programme with the haemophilia chapter in Lahore, Pakistan.
Since 1992 she is secretary-treasurer of the Dutch Haemophilia Treaters Society, member of the advisory board of the ministry of Health 'Haemophilia Platform', the advisory board of the Netherlands Hepatitis Foundation and the advisory board 'Hepatitis C and haemophilia'.

Meer, J. van der

Jan van der Meer studied medicine at the University of Groningen and graduated in 1974. He specialised in internal medicine in Groningen (board certified 1983), followed by a fellowship in haematology (board certified 1985). In 1994 he received his PhD at the University of Groningen on his thesis *Antithrombotic drug therapy to maintain graft patency after coronary artery bypass surgery*.
Since 1996 he has been associate professor of Haemostasis and Thrombosis, University of Groningen, and since 2002 professor of Vascular Medicine. He is head of the Division of Haemostasis, Thrombosis and Rheology, the Haemophilia Centre, and the Thrombosis Centre of the University Medical Centre Groningen. Professor Van der Meer is a member of several scientific boards, and reviewer and editor of several journals. He has published over 200 publications in peer review journals. He is currently a board member of the Dutch Haemophilia Treaters Society.

Meijer, K.

Karina Meijer graduated in 1996 from the University of Groningen. Subsequently, she worked in the Haemophilia and Thrombosis Centre at the University Medical Centre Groningen. In 2002, she received her PhD on her thesis *Liver disease and inherited or acquired coagulation disorders, Scylla and Charibdys of therapy*. She specialised in internal medicine in the Isala Clinics in Zwolle and in Groningen, and recently finished her haematology specialisation in the University Medical Centre Groningen. She currently works as a haematologist in the Haemophilia and Thrombosis Centre, with research interests in liver disease and atherosclerosis in coagulation disorders.

Novakova, I.R.O.

Irena Nováková studied medicine at the Charles University in Prague, Czech Republic, and graduated in 1967. From 1967 till 1969 she worked in the Český Brod Hospital (Czech Republic), at the department of surgery and later at the department of internal medicine. From 1969 till 1973 she specialised in internal medicine in the UMC St Radboud Nijmegen (board certified 1973) and board certified for internal medicine-haematology in 1975. She continued to work in the field of benign and oncological haematology. In 1993 she obtained her PhD degree at the University of Nijmegen on her thesis *Diagnostic and therapeutic aspects of infection in the granulocytopenic patient*. Nováková participates in patient care, teaching of medical students and postgraduates, and clinical research. Her main topics of research − in co-operation with H. Verbruggen and W. van Heerde − are the development and monitoring of factor VIII inhibitors, management of factor VII deficiency and the working mechanism of

activated factor VIIa. Since 2000 she is the medical director of the Haemophilia Care Centre at the Radboud University Nijmegen.

Peerlinck, K.

Kathelijne Peerlinck studied medicine at the University of Gent (Belgium) where she graduated in 1981. She received her Board Certificate in Internal Medicine in 1987 after residencies in Internal Medicine at the University Hospitals of Gent (Belgium) and Leiden (The Netherlands). She was introduced in the fields of Thrombosis and Haemostasis and Haemophilia care at the University Hospital of Leiden (prof.dr. E. Briët) where she was a lecturer at the Department of Haematology from 1987 to 1990. In 1990 she moved back to Belgium where she is a staff member at the University Hospitals of Leuven in the Department of Bleeding and Vascular disorders. In 1994 she received her PhD at the University of Leuven on her thesis titled *Von Willebrand's disease and Hemophilia*. Since 2003 she is the medical director of the Leuven Haemophilia Treatment Centre.

Posthouwer, D.

In 2002 Dirk Posthouwer graduated in medicine at the University of Utrecht. He became a Master of Science in Clinical Epidemiology at the Netherlands Institute for Health Sciences in 2005.
From January 2003 - March 2006 he worked as medical researcher in the Van Creveldkliniek, department of haematology, University Medical Centre Utrecht during which years he prepared his thesis *Hepatitis C among patients with congenital bleeding disorders*. He received his PhD in 2006. Since March 2006 he is resident internal medicine in the UMC Utrecht.
Posthouwer is the author of several articles on various aspects of hepatitis C in patients with haemophilia.

Smit, C.

Cees Smit studied business economics at the Free University in Amsterdam. From 1978 till now he has been a member of the research project 'Hemophilia in The Netherlands', Leiden University Medical Centre. From 1987 till 1998 he was co-ordinator of the Dutch National Haemophilia Patient Society, from 1998 till 2002 he worked in mental health care. At present, he is chairman of the Kwadraad Foundation, a foundation active in improving the quality of mental health care. Smit also chairs the Stichting Informatie Dierproeven [Foundation for Information on Animal Research].
Smit is a committee member of the Health Care Efficiency Research Programme (CDO) and the Translational Gene Therapy Programme of the Netherlands Organisation for Health Research and Development (ZonMw) as well as a member of the Advisory Council on Health Research (RGO) in the Netherlands. He is a honorary board member of the European Platform for Patients' Organisations, Science and Industry (EPPOSI) in Brussels.
In 2003 Smit received an honorary doctorate from the Council of Deans of the University of Amsterdam in recognition of his work on haemophilia and medical biotechnology.

Colophon

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