

Hemophilia on the treshold of the 21st century Plug, I.

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Chapter 2.1

Mortality and causes of death in patients with hemophilia, 1992-2001

A prospective cohort study

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Summary

We studied mortality, causes of death and life expectancy of hemophilia patients between 1992 and 2001. We compared these findings with those of previous cohorts, together spanning the periods before, during and after the use of potentially contaminated clotting products.

We performed a prospective cohort study among 967 patients with hemophilia A and B. Death rates, overall and cause-specific, were compared to national mortality figures for males adjusted for age and calendar period as Standardized Mortality Ratio (SMR's). Between 1992 and 2001, 94 (9.7%) patients had died and 2 patients were lost to follow-up (0.2%). Mortality was 2.3-times higher in hemophilia patients than in the general male population (SMR 2.3 95% confidence interval 1.9-2.8). In patients with severe hemophilia life expectancy decreased from 61 to 59 years. Exclusion of virus-related deaths resulted in a life expectancy at birth of 72 years.

AIDS was the main cause of death (26%) and 22% of deaths were due to hepatitis C. In patients not affected by viral infections mortality was still slightly higher than in the Dutch male population. Thus mortality of patients with hemophilia is still increased; this is largely due to the consequences of viral infections.

Introduction

Hemophilia is an X-linked genetic bleeding disorder caused by deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). Due to the hereditary pattern of hemophilia patients are almost invariably male, while women can be carriers of the disease. Severe forms are characterized by major bleeding occurring spontaneously or after minor trauma. These hemorrhages often occur into joints eventually causing disabling arthropathy¹.

Before the introduction of clotting factor preparations the mean life expectancy of patients with hemophilia was less than 30 years², and patients mostly died of intracranial³⁻⁵ or other hemorrhages. Since the 1960s factor VIII and IX preparations have been available for the treatment of hemophilia. This rapidly led to medical and social improvements, with a decrease in the frequency of hemorrhages and considerably improved life expectancy of patients with hemophilia.

Despite these positive developments, mortality of patients with hemophilia again increased during the 1980s. In 1982, the first case of acquired immunodeficiency syndrome (AIDS) in a patient with hemophilia was reported^{6,7}. Since then many more cases have been reported worldwide, of whom many have died. In addition, about 80 percent of the patients treated with clotting factor products before 1992 became infected with hepatitis C^{8,9}. The full consequences of hepatitis C infections are only recently being recognized¹⁰

Since 1985, products have been safe for HIV and since 1992 also for the transmission of hepatitis C (HCV). Today, the most important complication of clotting factor treatment is the development of neutralizing antibodies (inhibitors) against factor VIII or IX¹¹.

Few studies have reported on mortality in the total population of hemophilia patients after the period of the risk of viral infection transmission. Several studies have aimed at describing mortality within a specific subpopulation, such as hemophilia patients infected with HIV¹²⁻¹⁴. This study completes the inventory of mortality in patients with hemophilia over the last 30 years in the Netherlands, which describes the period before¹⁵, during¹⁶ and after the use of potentially contaminated clotting products.

Objectives

We studied mortality, causes of death and life expectancy of hemophilia patients between 1992 and 2001. We compared these findings with those of previous cohorts from our national surveys on hemophilia, starting in 1972.

Material and methods

Study design

A prospective cohort study was performed as part of a survey among all known patients with hemophilia in the Netherlands. In June 1992, we sent questionnaires to all patients who were listed with the Netherlands Hemophilia Society, with the hemophilia treatment centers, or on updated mailing lists from previous surveys in 1972, 1978 and 1985¹⁷. For this national study, 1292 patients received a questionnaire of whom 967 (75%) responded. Vital status at the end-of study date was determined by the response to the survey of 2001, from the attending physician or from municipal population registries. Of patients who had died during follow-up dates of death were obtained from municipal registries and physicians. This study is part of the Hemophilia in the Netherlands-5 study, which has been approved by the Committee of Medical Ethics of the Leiden University Medical Center.

Cause of death

The causes of death were obtained from treating physicians or general practitioners and were categorized according to the tenth revision of the International Classification of Diseases, Injuries, and Causes of Death-10 (ICD-10)¹⁸. Overall and cause-specific mortality of the general Dutch male population was retrieved from the Central Bureau of Statistics¹⁹. Date of birth, severity of hemophilia, HIV status and information on inhibitory antibodies were derived from the self-reported answers to the questionnaire. Severity of disease and type of hemophilia were verified with the patients' physicians. Severity of hemophilia, depending on the residual clotting factor activity was categorized as severe (< 0.01 IU/ml factor VIII or IX), moderate (0.01-0.05 IU/ml) or mild (>0.05-0.40 IU/ml factor VIII or IX). The HIV status was based on self-reported answers of the patients. If patients were born after 1985 or if they reported no treatment with clotting factor between 1979 and 1985, HIV status was considered to be negative.

Statistical analysis

Standardized Mortality Ratios (SMR's) were calculated to estimate the rate of overall and cause specific death of patients with hemophilia relative to that of the general male population adjusted for age and calendar period. The SMR is the number of observed deaths divided by the number that was expected if the mortality rate in the cohort, with its specific age-distribution, was the same as that in the general population. Patients were followed from the 1st of June 1992 to the 1st of July 2001. We used mortality rates from the Dutch general male population between 1992 and 2001. Ninety-five percent confidence intervals (CI) were based on a Poisson distribution for the observed number of deaths. To put our findings into perspective they were compared to those of the previous cohort studies between 1972-1985¹⁵ and 1985-1992¹⁶. For this comparison mortality ratios were calculated by direct

standardization using WHO standardization weight factors

(http://www3.who.int/whosis/discussion_papers/pdf/paper31.pdf).

Two methods were used to exclude the effect of viral infections on mortality 1) exclusion of patients who reported to be HIV positive in 1992 and 2) censoring patients of whom death was a result of HIV (AIDS) or HCV (liver cirrhoses, hepatocellular carcinoma) at the date of death. Cause-specific SMRs were calculated by studying the specific cause of death as endpoint and censoring patients with other endpoints. Median life expectancy was calculated with left truncated survival analysis and was expressed as the median age at which cumulative survival was 50%.

Results

Table 1 shows the general characteristics of the patients with hemophilia in 1992. Between 1992 and 2001 the total number of patient-years of follow-up was 8868 (mean 8.6 (range 0-9) yrs), 94 patients died and two patients were lost to follow-up. Of all 967 patients in the cohort, 796 (87%) patients had hemophilia A and 125 (13%) patients had hemophilia B; 386 (39%) patients had severe hemophilia, 167 (17%) patients had moderate hemophilia and 414 (43%) had mild hemophilia; the mean age was 32 (range 0-82) years; 50 (5.2%) patients reported to have inhibitory antibodies against the deficient clotting factor; and 53 patients (5.5%) were HIV positive. The mean age at death was 52 years, with a range from 14 to 83 years. In 20% of deceased patients the presence of an inhibitor was reported at time of death. The expected number of deaths during this same calendar period was 39. The standardized mortality ratio (SMR) was 2.3 (CI 1.9-2.8), indicating that the overall mortality rate of patients with hemophilia was two times higher than in the general male population. In patients with severe hemophilia was five times higher than expected, SMR 5.1 (CI 3.8-6.8).

	N=967
Age (yrs)	32 (0-82)
Severity of disease	
Severe (<0.01 IU/ml)	386 (40)
Moderate (0.01-0.05 IU/ml)	167 (17)
Mild (>0.05-0.40 IU/ml)	414 (43)
Type of hemophilia	
Hemophilia A	796 (87)
Hemophilia B	171 (13)
HIV infection	53 (6)
Inhibitor present [*]	50 (9)

Table 1. General characteristics of participants at entry (1992)

Data presented are means(range) or numbers(percentages) * Inhibitory antibodies against the deficient clotting factor

Standardized mortality ratios taking into account HIV infection and severity of disease are shown in Table 2. Restriction of the analysis to patients not infected with HIV revealed that mortality in patients with hemophilia was 70 percent higher than that in the general population (SMR 1.7, CI 1.3-2.7). After exclusion of deaths related to either HIV or HCV mortality rate among patients with hemophilia was 20 percent higher than among the general population (SMR 1.2, CI 0.9-1.6), in patients with severe hemophilia this was 40% (SMR 1.4,CI 0.8-2.4).

	Observed deaths [*] All patients		HIV negative patients [‡]	
		SMR $(95\% \text{ CI})^{\dagger}$	SMR (95% CI)	
All	94	2.3 (1.9-2.8)	1.7 (1.3-2.1)	
Severity				
Severily				
Severe	47	5.1 (3.8-6.8)	2.8 (1.9-4.2)	
Moderate	15	2.6 (1.5-4.3)	2.3 (1.3-3.9)	
Mild	32	1.3 (0.9-1.9)	1.2 (0.8-1.6)	
Type of hemophilia				
Hemophilia A	81	2.3 (1.9-2.9)	1.7 (1.4-2.2)	
Hemophilia B	13	2.3 (1.3-4.0)	1.3 (0.6-2.7)	

Table 2. Standardized Mortality Ratios (SMR) for severity and type of hemophilia taking into account the HIV status

^{*}Data presented are absolute numbers of observed deaths

[†]95% Confidence Interval

[‡]Only including patients who reported to be HIV negative or patients who were born after 1985

Direct standardization of mortality rates made comparisons between time periods possible. We found that mortality of the whole cohort of patients with hemophilia did not change over three time-periods. Relative rate, compared to subjects without hemophilia, i.e., the general population, was 1.6 between 1972 and 1985, 2.1 between 1985 and 1992 and it was 2.0 between 1992 and 2001. However, stratification for severity of hemophilia revealed that the rate of death of patients with severe hemophilia increased over the last three decades. It was three times higher than the rate in subjects without hemophilia during the period between 1985-1992 and it was 4.5 times higher during the last period of follow-up.

Cause specific mortality

Table 3 shows the primary causes of death between 1992 and 2001. Between 1992 and 2001 24 (26%) patients died of AIDS of whom 22 (87.5%) had severe hemophilia. In 21 patients (22%) death was due to a HCV infection; in two of these patients complications of a liver

transplantation were the cause of death, while in five patients a hepatocellular carcinoma or metastasis of a liver carcinoma was reported.

Cause of death (ICD-10 [*] Code)	1973-1986	1986-1992	1992-2001
	n=43 (%)	n=45 (%)	n=94 (%)
AIDS [†] (B20-34)	0 (0)	12 (27)	24 (26)
Hepatitis C	-	-	21 (22)‡
Hepatocellular carcinoma (C22)	-	-	5 (5)
Chronic liver disease (K70, K72.9, K73-K74, C78.7)	0 (0)	5 (11)	10 (11)§
Diseases of the circulatory system (I00-I99) Ischemic heart disease (I20-I25) Cerebrovascular disease (I60-I69)	4 (9) 1 (2) 3 (7)	10 (24) 0 (0) 9 (20)	16 (17) 6 (6) 4 (5)
Malignancies (C00-D48)	13 (30)	7 (15)	12 (15)
Hemorrhages	20 (47)	1(2)	5 (5)
Other (A40.3, A41.9, J18, R06.8, R54) or not natural cause of death (T14.9, V01-Y98)	3 (5)	6 (9)	13 (11) [∥]
Sudden death, cause unknown (R96, R99)	3 (7)	4(9)	3 (3)

Table 3. Primary causes of death according to the ICD-10 classification

*ICD-10=International Classification of Diseases, 10th revision,

 $^{\dagger}AIDS = Acquired ImmunoDeficiency Syndrome$

[‡]2 patients due to complications of livertransplantation, 5 of hepatocellular carcinoma, 10 of chronic liver disease, in four patients only hepatitis C mentioned as cause of death

[§] In four patients a hemorrhagic shock was reported

¹1 patient died due to 'natural causes',

A hemorrhagic shock resulting from end-stage liver disease (n=10) was reported in five patients. A co-infection with HIV and HCV was observed in five of the deaths resulting from hepatitis C. Mortality due to AIDS and chronic liver disease was highest in patients with severe hemophilia although these causes of deaths were also observed in patients with

moderate hemophilia (n=4, 27%). Among patients in whom death was not related to HCV or HIV (n=49) the main cause of death was hemorrhage (13/49), which also includes intracranial hemorrhages (n=4) and hemorrhages resulting from trauma (n=4). Compared to the Dutch male population the incidence of death from intracranial hemorrhages is higher in patients with hemophilia, 0.1 per 1000 person-years and 0.5 per 1000 person years respectively. Death from malignant neoplasm (including hepatocellular carcinoma) was reported in 22% of patients. Although the percentage of patients with mild hemophilia that died as a result of malignancies was higher than in the Dutch male population, at 41% vs. 31%, overall mortality of malignancies was lower, at 19% vs. 31%. Death due to disease of the circulatory system was lower in patients with hemophilia than in the Dutch male population 17% and 28% respectively. The cause of death remained unknown in three patients.

The proportion of patients that died of AIDS stayed constant during the last two periods of follow-up. Death due to hepatitis C increased compared to the period between 1985 and 1992, 11% vs. 22%. No deaths of AIDS or hepatitis C were reported in the first period of follow-up (1972-1985). The occurrence of cerebral vascular disease was lower than in 1986-1992, when it accounted for 20% of all deaths compared to 4% in the current period of follow-up.

In Table 4 cause-specific standardized mortality ratios are shown. Mortality due to viral infections was 117 times higher than in the general population, and mortality due to HCV was 16 times (SMR 16.1, CI. 7.7-33.8) higher in patients with hemophilia than in the general population.

Cause of death (ICD-10 Code)	Observed [*]	SMR $(95CI)^{\dagger}$
AIDS (B20-B24)	24	117.2 (77-178)
Hepatitis C		
Hepatocellular carcinoma (C22)	4	17.2 (5.2-35.9)
Chronic liver disease (K70, K72.9, K73-K74)	10	16.1 (7.7-33.8)
Ischemic heart disease (I20-125)	6	0.5 (0.2-1.1)
Cerebrovascular disease (I60-I69)	4	1.0 (0.2-2.2)
Malignancies	18	1.5 (1.0-2.5)
Malignancies (no liver)	12	1.1 (0.6-1.9)

Table 4. Primary cause of death specific Standardized Mortality Ratios

*Absolute numbers of death observed

[†] 95% Confidence Interval

Life expectancy

Life expectancy was calculated stratified for severity of hemophilia and based on extrapolation from the observed death rates (Table 5). In patients with severe hemophilia a life expectancy of 59 years at birth was observed, and censoring of patients that died due to virus infections resulted in a life expectancy of 71 years in patients with severe and moderate hemophilia. Life expectancy at birth of patients with mild hemophilia was lower than that of the male population, at 73 years compared to 76 years. After exclusion of viral infections the life expectancy of mild hemophilia patients was 75 years.

The overall life expectancy of the patients with hemophilia did not notably change between 1972 and 2001. The life expectancy of patients with severe hemophilia, however, decreased

from 63 to 59 years. For patients with moderate hemophilia life expectancy increased from 65 to 67 years.

	1972-1985	1985-1992	1992-2001		
			All patients	HIV negative*	HIV and HCV^{\dagger}
			N=967	N=511	negative
					N=967
All patients (years)	66	68	67	70	74
Dutch males	71	74	76	76	76
Severity of hemophilia					
Severe	63	61	59	70	71
(<0.01 IU/ml)					
Moderate	65	65	67	71	75
(0.01-0.05 IU/ml)					
Mild	-	74	73	73	75
(>0.05-0.40 IU/ml)					
Туре					
Hemophilia A	-	69	68	70	73
Hemophilia B	-	64	60	73	‡

Table 5. Life expectancy (years) according to severity in 30 years of follow-up

* Patients of whom HIV status was negative or who were born after 1985 † HIV and HCV related deaths are censored * Not available due to limited numbers

Discussion

During the last decade hemophilia was characterized by an excess mortality as compared to the general population. Human Immunodeficiency Virus (HIV) infection was responsible for the largest number of deaths (n=24, 26% of deaths) and 16% of deaths were due to hepatocellular carcinoma or chronic liver disease resulting from a HCV infection. Overall, patients with severe hemophilia had a five-fold higher risk of death than men in the general population. Without the effects of HIV and HCV the rate of death among patients with severe hemophilia was 1.4-fold higher than expected. The remaining excess risk in all likelihood results from hemorrhages. Life expectancy of patients with severe hemophilia not affected by hepatitis C or HIV had a life expectancy of 71 years, which can be compared to a life expectancy of the Dutch male population of 76 years.

In the survey of 1992, 93% of all Dutch hemophilia patients were sent a questionnaire, of whom 75% participated in the survey, and were subsequently followed for this study on mortality. Only two patients were lost to follow-up and we were able to retrieve 96% of all causes of death. This resulted in a complete cohort comprising a large population of hemophilia patients. There was no difference in severity of hemophilia or mean age between the responding and non-responding population to the questionnaire of 1992, and therefore we consider our data to be generalizable to the Dutch hemophilia population. Theoretically, because the causes of death were reported by the treating hematologist or the general practitioner there may have been discrepancies with the general population data gathered through the Central Bureau of Statistics. We do not expect this to be of large influence. As always in research on life expectancy the findings may not hold for the present patients with hemophilia. Exclusion of effects of viral infections results in a reflection of the situation for patients not exposed to non-safe clotting products or not infected products. In our cohort no

deaths were reported in the youngest age-category between 0 and ten years. The youngest participant to this study was four months old, and therefore our study did not cover perinatal mortality. Due to limited information on the presence of inhibitory antibodies we have not been able to study the impact on mortality.

Our study shows a two-fold increased mortality for patients with hemophilia; in patients with severe hemophilia this was even a five-fold increase. We estimated the future perspective by excluding death due to HIV or hepatitis C. There still appeared to be a trend towards a moderately but enduring increased mortality for patients with hemophilia, especially in severe hemophilia. As nowadays products are safe from transmission of HIV and hepatitis C, preventive efforts should focus on factors causing this remaining excess mortality. The most important factor is an increased risk of death of hemorrhages, either intracranial or resulting from trauma. Although mortality of HCV and HIV is extensive and the numbers to compare with the general population are limited there seems to be a higher incidence of death from intracranial hemorrhages in patients with severe, moderate and mild hemophilia. This indicates the importance of adequate and specialized care for hemophilia patients. Although we also observed a high number of other hemorrhages, e.g., resulting from trauma we were not able to make a comparison with the general population. A second factor of impact could be deaths due to hepatitis C that had not been reported as such. However, as the hepatitis C status is well known and a good registration is used by treating physicians this is probably of limited influence

Over the last three decades causes of death of patients with hemophilia have changed; during the 1970s and early 1980s patients with hemophilia died mostly of intracranial hemorrhages, while during the late 1980s AIDS became the main cause of death. Although in the

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Netherlands the impact of HIV was relatively low through the use of predominantly products from local voluntary unpaid donors, AIDS was responsible for a quarter of all deaths during the 1990s. In the present follow-up period about 80% of deaths from AIDS occurred before 1995, indicating that the impact of AIDS on mortality of patients with hemophilia is declining. This decreased influence is explained by a reduced number of survivors of an HIV infection, and by improved survival of patients infected with HIV through HAART therapy 20 . The effects of hepatitis C infections on mortality have increased considerably during the last ten years, and about 20% of deaths were due to the effects of hepatitis C, of which liver cirrhosis or liver failure were the most prevalent. Our study shows a highly increased risk of death of hepatocellular carcinoma, which is similar to a study by Darby et al in which a 20fold increased risk was reported in non-HIV infected patients with severe hemophilia²¹. Although the introduction of new treatment methods combining pegylated interferon with ribavirin will positively influence mortality of HCV infected patients the effects of HCV will remain to be present in those patients in whom this therapy failed. For patients not affected by viral infections hemorrhage was still a relatively frequent cause of death. As this is similar to the period before the impact of viruses transmitted by clotting products we might conclude that the increased availability of clotting factor has not reduced the number of deaths due to hemorrhages. The number of deaths from malignant neoplasm was not higher than expected in this population. In concordance with earlier studies and findings by Rosendaal et al we observed a reduced rate of mortality of ischemic heart disease in patients with hemophilia²².

Life expectancy of patients with severe hemophilia was lower during the last decade as compared to earlier observations. An important part of this decline is explained by death due to viral infections. When AIDS and hepatitis C deaths were excluded, life expectancy, improved but although the general life expectancy in European countries is approached it remains to be lower especially in patients with severe hemophilia ²³. Walker et al published the same observations in a Canadian population²⁴. After exclusion of viral infections patients with mild and moderate hemophilia have a life expectancy that is about equal to the average Dutch male population.

Our data show that HIV and hepatitis C still largely influence mortality of hemophilia patients. The effects of hepatitis C will be present for many years to come. In patients with severe hemophilia not infected with viruses mortality is still 40 percent higher than in the general population. Although this suggests that the current patient with hemophilia benefits from safe clotting products life expectancy is still negatively influenced by this bleeding tendency.

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