

Treatment of haemophilia in the elderly

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Keywords

Haemophilia A, co-morbidity, ageing

Summary

Treatment of elderly patients with haemophilia is an upcoming challenge in haemophilia care. We included patients with haemophilia A older than 60 years of age, who visited our haemophilia centre between 2006 and 2008. We conducted a retrospective study focussing on the patients' co-morbidities as well as changes in their bleeding patterns between 2003 and 2008. **Results:** There is a tendency of increasing bleeding symptoms with increasing age of the patients due to more frequent spontaneous joint bleedings, malignancies or treatment with phenprocoumon or ASS. In consequence, FVIII dosage had to be increased for 8 patients (28%). Chronic hepatitis C, coronary heart disease and malignancies are the most frequent co-morbidities

Schlüsselwörter

Hämophilie A, Komorbidität, Alter

Zusammenfassung

Die Behandlung von Patienten mit Hämophilie im Alter stellt eine besondere Herausforderung dar. Wir studierten die klinischen Erscheinungsformen bei Patienten mit Hämophilie A, die älter als 60 Jahre sind und unser Hämophiliezentrum in den Jahren 2005 bis 2008 aufsuchten. Retrospektiv untersuchten wir die Komorbiditäten sowie die Veränderungen der Blutungsfrequenz und -intensivität in den Jahren 2003 bis 2008. **Ergebnis:** Tendenziell war eine Zunahme der Blutungssymptome mit dem Alter aufgrund gehäufte spontaner Gelenkeblutungen, maligner Erkrankungen oder der Behandlung mit Phenprocoumon und Azetylsalizylsäure zu verzeichnen. Deshalb musste die Dosierung des Faktor-VIII-Präparats bei 8 Patienten (28%) erhöht werden. Als häufigste Komorbiditäten traten chronische Hepatitis C, koronare Herzerkrankung und maligne Erkrankungen auf.

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Hämophilie-Behandlung bei älteren Patienten Hämostaseologie 2009; 29 (Suppl 1): S29–S31

The population of elderly haemophilia patients increased with the advent of coagulation concentrates and the introduction of highly active antiretroviral therapy (HAART). The increasing numbers of co-morbidities related to higher age and their treatment constitute a challenge in the treatment of patients with haemophilia. However, there is only little experience with treatment patterns of haemophilia in elderly patients. Nevertheless, physicians must handle age-related clinical problems never previously ob-

served in this population. There are only several studies concerning the life expectancy of haemophiliacs dependent on the time period, region and virus infection (► Tab. 1) (1–4).

While life expectancy of haemophiliacs with HIV-related diseases decreased, exclusion of virus-related deaths resulted in an increasing life expectancy. Following the introduction of HAART, deaths due to AIDS have decreased. The Canadian experience showed that 27.2% of 2427 Canadians with haemophilia were HIV-positive, of whom 61.5%

died between 1980 and 2001. In contrast, 6.5% deaths occurred in HIV-negative controls (5). Life expectancy of haemophiliacs in the USA decreased from 55 years (1979–1982) to 40.5 years (1987–1990), and increased again to 46 years (1995–1998). In the period 1995–1998, the median age of haemophilia A decedents with HIV-related disease was 33 years, compared to 72 years for those without HIV-related disease (3). In patients with severe haemophilia in The Netherlands, life expectancy decreased from 63 (1972–1985) to 59 years (1992–2001).

Exclusion of virus-related deaths resulted in a life expectancy at birth of 72 years (2). HAART has reduced HIV progression and AIDS associated mortality in haemophilic men, which has resulted in an increase in the cumulative incidence of non AIDS-related mortality. At the same time mortality from liver diseases, including liver cancer, was substantially increased compared with mortality in the general population. This would be expected given the high rates of infection with hepatitis C virus (HCV) in the haemophilia population through replacement therapy with inadequately or non-virus-inactivated clotting factor products during the 1970s and 1980s (7).

With the advent of recombinant coagulation concentrates and virus inactivation procedures, virally safe products for HIV and virally safe products for HCV have been available. As a consequence, the population of elderly haemophilia patients increased, which is also due to the improvement of replacement and antiviral therapy.

Methods

We included patients with haemophilia A older than 60 years of age, who visited our haemophilia centre between 2006 and 2008. We conducted a retrospective study focussing on co-morbidities as well as changes in bleeding patterns between 2003 and 2008.

Results

29 patients were included with a median age of 64 years (60–85 years). 8 suffered from se-

vere haemophilia A (<1% FVIII:C), 7 from moderate haemophilia A (1–5% FVIII:C) and 14 from mild haemophilia A (>5% FVIII:C). Seven patients died during the ob-

serva-tion time. Causes of death: hepatocir-rhosis (n= 3), hepatocellular carcinoma (n = 1), plasmocytoma (n = 1), heart failure (n = 1), and one case remained unclear (▶Tab. 2). In total, 57% of deaths were caused by hepatic diseases.

All of the 29 elderly haemophilia A pa-tients had at least one co-morbidity or risk factor like hypertension or diabetes. Of 20 HCV-positive patients: in 2 patients infec-tions cleared after treatment and 18 patients developed chronic hepatitis C. 14% of the pa-tient cohort died of liver related diseases dur-ing the five years of study. One patient suf-fered from chronic hepatitis C and HIV. Two patients had a factor VIII inhibitor. Nine pa-tients suffered from cardiac disease, primarily coronary heart disease. Four patients received ASS and two patients phenprocoumon. Eight patients suffered from malignancies, pri-marily hepatocellular carcinoma, prostate cancer and colon cancer.

In eight patients (median age: 69.5 years, 58–84 years) a change of bleeding patterns was noted, with a subsequent change of the substitution regime and an increase of factor concentrate dosing. In two patients frequency of prophylactic treatment had to be in-creased. Two other patients who were treated on demand needed temporary prophylaxis. Three patients were switched from on de-mand treatment to long term prophylaxis. One patient who had not received factor sub-stitution before started on demand treat-ment.

The change of bleeding patterns was mainly caused by more frequent spontaneous joint bleeding in severe haemophilia (n = 3) or underlying malignant disease (n = 5) in se-vere, mild and moderate haemophilia. Two of the concerned patients were treated with ASS or phenprocoumon (▶Tab. 3). The change of dosing was necessary at the median age of 69.5 years (58–84 years). An increase of bleedings and factor replacement was re-ported in the majority of patients with severe haemophilia (5/8, 62%), majority of patients with malignancies (5/8, 62%), majority of patients who died during study (5/7, 72%) and one of two patients with phenpro-coumon (indication: atrial fibrillation with arrhythmia) and one of four patients with ASS (indication: coronary heart disease).

Tab. 1 Life expectancy change depending on time period, region and virus infection

first author, year (ref.)	region	time period	life expectancy (years)
Rosendaal, 1989 (1)	The Nether-lands	1973–1986	66
Plug, 2006 (2)	The Nether-lands	1972–1985	severe haemophilia 63
		1985–1992	61
		1992–2001	59 (72 HIV/HCV-)
Chorba, 2001 (3)	USA	1979–1982	55
		1987–1990	40.5
		1995–1998	46 (33 HIV+, 72 HIV-)
Darby, 2007 (4)	United Kingdom		severe haemophilia 63 (HIV-) moderate/ mild haemophilia 75 (HIV-)

patients enrolled 2006–2008	29
severity of haemophilia	
severe <1 %	8
moderate 1-5 %	7
mild 5-50 %	14
median age	64 years (60–85)
history of FVIII inhibitor	2
cause of death during study	3 hepatocirrhosis 1 hepatocellular carcinoma 1 heart failure 1 plasmocytoma 1 reason unclear

Tab. 2 Patients' characteristics

	patient 4	patient 5
severity of haemophilia	mild	moderate
anticoagulation	marcumar	ASS
reason for anticoagulation	atrial fibrillation with arrhythmia	myocardial infarction
cardiovascular risk factors	hypertension, BMI 26 kg/m ²	
reason for change of FVIII dosage	haematuria	haematuria, gastrointestinal bleeding
age at treatment change	74 years	84 years
change of treatment	on demand to prophylaxis	none to on demand
co-morbidities	carcinoma of prostate, chronic hepatitis (HCV)	carcinoma of colon and bladder, chronic hepatitis C

Tab. 3 Characteristics of patients with increased bleeding and phenprocoumon or ASS treatment

Discussion

There is not much of experience in the treatment of elderly haemophilia A patients. Even if our patient population at the age = 60 years is very small and no statistical evidence can be shown, we try to outline upcoming developments and possible clinical situations especially for haemophilia A.

In our cohort we observed that three of eight patients with severe haemophilia had more frequent spontaneous joint bleedings and required an adjustment of treatment through increased dosing of factor concentrates. This is an unexpected observation because spontaneous bleedings into joints were rather seen in the age of childhood and adolescence.

Two patients who received ASS or vitamin K antagonists needed increased factor VIII replacement due to haematuria. There is an urgent need for dose-finding studies and for analysis of the risk benefits of antiplatelet and anticoagulation therapy in haemophilic patients with thrombotic risks. In addition, further studies are needed to evaluate if the risk of apoplexy following arrhythmias in haemophiliacs is different from non-haemophiliacs. Therapeutical consequences like reduction of dosage or different therapies to avoid or to treat apoplexy need to be established and discussed.

Another cause of increased replacement therapy was underlying malignant disease in five patients independent of severity of haemophilia. A potential correlation of malignant diseases to haemophilia patients with HCV infection needs further evaluation.

In our cohort a reduction of bleeding symptoms or dosage of FVIII was not observed. There is a tendency of increasing bleeding symptoms and FVIII dosage with increasing age.

In total, 28% of the elderly patients needed a dose FVIII adaption, because of increased demand.

This change of bleeding patterns concerned the majority of patients with severe haemophilia, with malignancies and those who died during study period.

Conclusion

The treatment of elderly patients with haemophilia is an challenge in haemophilia care.

- Increasing numbers of joint bleedings in severe haemophilia A and bleeding tendency due to malignant diseases or treatment with anticoagulants require increasing dosing of factor concentrates.

- Chronic hepatitis C, coronary heart disease and malignancies are the most frequent co-morbidities.

Treatment of HCV infection and terminal liver disease has become the future challenge in this population.

Conflict of interest

All authors declare, that there is no conflict of interest.

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