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REVIEW ARTICLE

Challenges and controversies in haemophilia care in adulthood

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Summary. Overall life expectancy and quality of life among persons with haemophilia have increased in recent years, primarily because of the advances in factor replacement therapy and better treatment of infectious diseases. Older haemophilic patients now face aging co-morbidities that are common in the general male population, such as cardiovascular or metabolic diseases, prostate hypertrophy and hepatic, prostate and other cancers. The prevalence of cardiovascular disease and incidence of vascular events among older haemophilic patients can be expected to increase and haemophilic patients may become prone to some cardiovascular risk factors, warranting preventative measures. The treatment of long-term complications of hepatitis C virus infection such as liver cirrhosis and hepatic cancer can be expected to be required in a large portion of the older haemophilia population for some years to come. Appropriate antiviral treatment and close monitoring for possible disease advancement will constitute an important part of routine medical care, and special considerations may be appropriate in conjunction with invasive procedures, chemo- or radiotherapy. At the moment, hard data on which to base the management of these conditions are largely lacking, but can be expected to increase dramatically in the coming decades. In the meantime, the ageing population of haemophilia patients should be offered the same comprehensive health care offered to the general population, which may require a restructuring of health care delivery.

Keywords: adults, cancer, cardiovascular risk, haemophilia, HCV, HIV

Introduction

In the past, routine haemophilia care focused primarily on paediatric patients because of the high morbidity and mortality associated with the disease in young children [1,2]. Advances in haemophilia care during the 1960s and 1970s, including the introduction of replacement therapy with factor concentrates, resulted in a considerable increase in life expectancy for persons with haemophilia [3,4]; however, the blood product-borne viral epidemics that decimated the haemophilia patient community in the 1980s and early 1990s had a negative impact on overall life expectancy [3]. Today, the prospect of new blood product-associated viral infections has been virtually eliminated and major improvements in the treatment of existing viral infections have been made. While patients with severe haemophilia still have a reduced life expectancy, the overall life expectancy of haemophilia patients is again approaching that of the general male population (Table 1) [4,6,9]. With the introduction of prophylactic treatment regimens during childhood and, increasingly, continuation of some level of prophylactic treatment during adulthood, the general state of health among persons with haemophilia is also beginning to resemble that of the overall population [10,11].

At present, 8% of haemophilia patients in Italy are aged more than 65 years, a trend that is likely to

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Table 1. Life expectancy among severe haemophilia patients.

Reference	Population	*n*	Calendar period	HIV status	Life expectancy (years)	
					Severe haemophilia	Overall male population
Darby *et al.* [4]	UK	2706	1977–1998	HIV–	63	78
Chorba *et al.* [5]	USA	2254*	1979–1982	All	55*	–
			1987–1990	All	41*	–
			1995–1998	All	46*	–
				HIV+	33*	–
				HIV–	72*	–
Plug *et al.* [6]	The Netherlands	386	1972–1985	All	63	71
			1985–1992	All	61	74
			1992–2001	All	59	76
				HIV–	70	76
Triemstra *et al.* [7]	The Netherlands	381	1986–1992	All	61	74
Rosendaal *et al.* [8]	The Netherlands	717	1973–1986	All	66	74
Larsson *et al.* [1]	Sweden	948*	1961–1980	All	57	76

*Figure includes all disease severities.
(–) No data provided.

continue [12]. Similar demographic shifts in other countries may force the medical community to re-evaluate the delivery and extension of comprehensive medical care for haemophilia patients to include the management of the diseases of older age. At the moment, hard data on which to base the management of these conditions are largely lacking, but can be expected to increase dramatically in the coming decades.

Possible scenarios for an ageing haemophilia population

In the past, disease-associated orthopaedic issues, bleeding risk and concerns about infectious agent transmission dominated the management of patients with haemophilia. The risk of new human immunodeficiency virus (HIV) and hepatitis C virus (HCV) transmission is greatly reduced with plasma-derived factor concentrates, and recombinant proteins avoid this issue entirely. The risk of variant Creutzfeldt–Jakob disease or unknown infectious agent transmission remains a concern and supports present efforts to develop improved factor concentrates and to optimise treatment regimens.

The potential benefits of terminating prophylactic factor replacement therapy such as convenience and cost savings must be balanced with the potential risks, which include joint damage as a result of even a small number of bleeds and/or subclinical bleeding, which may be exacerbated by age-related changes in joint synovia or cartilage [13]. Many adults appear to be using prophylactic replacement therapy at some level to facilitate employment, physical and social activities, thereby improving orthopaedic and social outcomes over time [14–20].

Table 2. Estimated number of haemophilia patients alive and infected with HIV or HCV. Adapted from Angelotta *et al.* [21].

Country	Number of persons with haemophilia		
	Total	HCV (%)	HIV (%)
USA	14 886	4456 (30)	1698 (11)
UK	6109	2829 (46)	405 (7)
Italy	5319	4361 (82)	534 (10)
Japan	4683	2436 (52)	871 (19)
France	4000	2600 (65)	1250 (31)
Canada	2772	1100 (40)	251 (9)
Australia	1070	534 (50)	84 (8)
Ireland	545	157 (29)	37 (7)
Total	39 384	18 473 (47)	5130 (13)

HCV, hepatitis C virus; HIV, human immunodeficiency virus.

The treatment of HIV and HCV infections will continue for a number of years and improved therapies have extended life expectancies dramatically, allowing the epidemiological emergence of HIV-associated lymphomas and HCV-associated liver cirrhosis and hepatocarcinomas (Table 2) [4,6]. In addition to existing HIV and/or HCV infections, alloantibodies and disease-related premature arthritis, older patients are prone to falls, cardiovascular and metabolic diseases, genitourinary problems such as prostate hypertrophy, osteoporosis, renal insufficiency and prostate, hepatic and other cancers [22]. Carcinoma (16%), bacterial infection (16%) and ischaemic heart disease (10%) are now the most common causes of death other than bleeding among haemophilia patients in the UK [23].

Challenges in the management of haemophilic arthropathy

The pathogenesis of haemophilic arthritis includes three stages: acute haemarthrosis, chronic synovitis and degenerative arthritis. Bleeding into joints stimulates an inflammatory response, synoviocyte hyperplasia and the resulting deposition of iron (reviewed in [24]). This phase can be treated using clotting factor concentrates to stop the bleeding and arthrocentesis to remove blood deposits. A large or poorly-treated joint bleed may lead to chronic synovitis, in which the synovium adopts a villous-like structure and predisposes the joint to further bleeding episodes [25]. Bleeding may be prevented or stopped using clotting factor concentrates; however, attempts to suppress synoviocyte hyperplasia have met with little success. The resulting cartilage loss is mediated by panus formation on the joint periphery, central neutrophil sequestration, release of metalloproteinases and eventual apoptosis of chondrocytes [25].

Chronic haemophilic arthritis is defined as the presence of chronic synovitis for >6 months and represents the end-stage of cartilage loss with osteophyte formation [26]. At this stage, the goal of treatment is to relieve symptoms using analgesia and to improve functional joint capacity with surgical interventions. The management of chronic haemophilic arthritis requires a team approach that includes a rheumatologist. Functional outcome studies over the years have clearly shown that prophylactic treatment reduces the number and severity of joint bleeding episodes, resulting in better functionality [27]. Radiological assessments have also shown that subclinical bleeding can result in joint damage and can be prevented with appropriate prophylactic treatment [13]. Furthermore, full prophylactic rather than intermediate or on-demand treatment regimens can hinder the progression of existing joint damage (reviewed in [24]).

Cardiovascular risk management and thromboembolic prophylaxis in the elderly patient

Data are lacking on the risk of cardiovascular disease in haemophilia patients, largely because of the early death of the previous generations of patients; however, the number of haemophilia patients with cardiovascular diseases, while lower than the general population, appears to be increasing (Table 3) [4,6–8,10,28,29] and detailed epidemiological studies are warranted as the population ages. In the meantime, the ageing population of haemophilia patients should be offered the same preventative cardiovascular health care offered to the general population, which may require a restructuring of health care delivery that involves a team approach between haematologists, general practitioners and cardiologists familiar with the special needs of haemophilia patients, or the assumption of primary care functions by haemophilia treatment centres.

The incidence of hypertension, smoking and diabetes may be higher in haemophilia patients than in the general male population [10,30–33]. In addition, a positive association between antiretroviral therapy and cardiovascular events has been observed among the general population [34–36] and may be applicable to the haemophilia population as well. Routine preventive care should therefore include a reduction of cardiovascular risks [10,33] and the lack of routine medical care provided by specialized haemophilia treatment centres may miss the opportunity to modify patient behaviour and avoid some cardiovascular risk factors.

Although haemophilia has long been considered protective for the development of atherosclerosis, there are conflicting data (Table 4) [28,37–41] and a number of reports have been published describing vascular events in patients with haemophilia [42–44]. A murine haemophilia model showed reduced atherosclerotic lesions that were nearly devoid of

Table 3. Cardiac mortality in haemophilia patients. Adapted with permission [28].

Reference	Calendar period	*n*	Observed deaths	Observed deaths per 1000 patients	Expected deaths	Standard mortality ratio (SMR)
Rosendaal *et al.* [8]	1973–1986	717	1	1.4	5	0.2
Koumbarelis *et al.* [29]	1972–1993	531	1	1.9	4	0.25
Triemstra *et al.* [7]	1986–1992	919	1	1.1	5.2	0.2
Plug *et al.* [6]	1992–2001	967	6	6.2	12	0.5
Darby *et al.* [4]	1977–2000	6018	104	17.3	166.5	0.62

Table 4. Intima media thickness as a measure of atheroschlerotic risk in haemophilia patients compared with the normal population. Adapted with permission [28].

Reference	*n*			Mean age	Outcome measured	Differences
	Haemophilia	vWD	controls			
Bilora *et al.* [37]	76	–	77	58.2	Plaque	Yes
Sramek *et al.* [38]	59	17	142	48.8	IMT	No
Bilora *et al.* [39]	25	15	40	48.3	Plaque	Yes
Bilora *et al.* [40]	50	–	50	41.7	Plaque	Yes
Sartori *et al.* [41]	40	–	40	39.5	IMT	No

vWD, von Willebrand disease; IMT, intima media thickness.

fibrin(ogen) and platelets at an early stage and delayed disease progression, but no difference in composition compared with wild type mice at later stages [45], suggesting that haemophilia may provide partial protection against atherosclerotic lesions. In addition, elevated factor VIII (FVIII) levels are associated with thrombotic events and FIX knockout mice are less prone to thrombus formation [46,47], therefore, while FVIII or FIX deficiencies do not appear to offer full protection against atherosclerosis, haemophilia may offer some protection against acute thrombotic occlusion of atherosclerotic vessels [4,6,38]. The association between arterial hypertension and the risk of intracerebral haemorrhage suggests that prophylactic replacement therapy in these patients may be prudent [4,48].

Procedures that usually require anticoagulation, such as cardiopulmonary bypass and valve replacement, necessitate special management in patients with bleeding disorders. Older patients who receive intensive replacement therapy, bypassing agents or who suffer from milder disease may be at particular risk of thrombotic events and appropriate anticoagulation therapy may need to be considered [43]. In general, cardiac valve replacement may require the employment of bioprosthetic rather than metal valves to avoid anticoagulation and bare metal stents may be more suitable than drug-eluting stents in coronary interventions to avoid prolonged dual antiplatelet therapy.

Management of haemophilia patients with hepatitis C virus

More than 90% of haemophilia patients in Western countries who received clotting factor concentrates prior to 1985 became infected with HCV and more than 50% of these patients were also co-infected with HIV [49]. HCV infection is associated with a high rate of chronic viral persistence with progression to liver cirrhosis and ultimately to liver cancer. This risk is particularly high in HIV/HCV co-infected individuals. As a result, hepatitis C has become a leading cause of mortality in haemophilia patients [50].

To prevent the complications of chronic hepatitis, patients with haemophilia should be offered HCV-directed antiviral treatment and individually tailored combination therapy with pegylated interferon and ribavirin constitutes the current backbone of anti-HCV treatment. Rapid viral clearance below the level of detection within 4 weeks of treatment has a high prognostic value that predicts sustained viral elimination, whereas a less than 100-fold decline in viral RNA at week 12 heralds treatment failure [51]. In general, HCV patients infected with viral genotypes 2 and 3 exhibit a better response and can be treated with short-term 16-week protocols if baseline viral loads are low and a rapid loss of detectable HCV-RNA (<4 weeks) is observed, thereby limiting drug exposure and side effects [52–54]. Patients infected with genotypes 1 or 4–6, however, should be treated for 12 months or longer if the patient shows a delayed response [55]. Patients who fail to respond to interferon therapy can benefit from anti-HCV re-treatment, if primary anti-HCV treatment was sub-optimal in any respect.

A treatment success rate of approximately 50% is observed if undetectable HCV levels are achieved within with 12 weeks of re-treatment and treatment in this case should be continued. Patients who have detectable virus after 12 weeks of re-treatment should discontinue the treatment, because the chance of achieving a sustained virological response is minimal. Patients with persisting HCV replication should be monitored regularly to detect early complications of disease progression, particularly hepatocellular carcinoma.

In addition to anti-HCV therapy, patients with HIV co-infection should receive highly active antiretroviral therapy, which markedly reduces their increased risk of HCV disease progression to about the same level as in HCV mono-infected patients [56]. On average, sustained viral elimination can

now be achieved in 60% of HCV-infected and 40% HCV/HIV-co-infected patients [57].

Patients who remain HCV-RNA-negative 6 months after the end of therapy have a minimal risk of disease recurrence and are considered sustained viral responders [58]. Nevertheless, these patients should continue regular antiviral surveillance. In particular, patients who have reached the stage of cirrhosis maintain a high risk for liver cancer and should be surveyed closely to detect hepatic malignancy at an early curable stage [59,60].

Liver transplantation has now been established as therapeutic option for HCV as well as HIV/HCV co-infected patients with terminal cirrhosis or early liver cancer and has the added benefit of correcting the clotting factor deficiency. Unfortunately, re-infection of the graft is common and antiviral re-treatment may be required [61]. Although a complete cure is not currently possible in every individual, modern antiviral therapy and treatment of HCV-related liver disease have considerably improved prognoses in haemophilia patients with HCV infection.

Management of cancer in persons with haemophilia

The incidence of cancer is increasing as the haemophilia population ages [4,10]. Hepatocarcinomas associated with HCV infection [50] and HIV-associated lymphomas [62,63] can be expected to maintain the prevalence of these carcinomas among virus-infected haemophilia patients for some time to come [10]. At present, there is no evidence that other cancers are more prevalent among patients with haemophilia than in the general population; however, the available data are limited to a handful of case reports.

In rare cases, unusual cancer-associated bleeding may lead to the diagnosis of milder forms of haemophilia. On the other hand, clinicians should beware of misdiagnoses in haemophilia patients with leukaemia and severe haemorrhagic symptoms [64], soft tissue tumours [65] or other primary malignancies [66] that are mistaken for pseudo-tumours.

The management of cancer in patients with haemophilia is supported by few data and complicated by the potential risks of bleeding associated with some invasive diagnostic or therapeutic procedures and chemotherapy-induced blood cell toxicity or haemostatic disturbances. In general, diagnosis and treatment should be implemented as in any other patient. Factor replacement therapy may be required in conjunction with invasive diagnostic procedures such as biopsies using a multidisciplinary approach in collaboration with haemophilia specialists. Radiological interventions may be associated with bleeding [67] and appropriate precautions should be undertaken to minimize bleeding risk.

Chemotherapy may present special risks for haemophilia patients caused by therapy-induced thrombocytopaenia and disseminated intravascular coagulation associated with infection. As a result, patients with inherited bleeding disorders are nearly always excluded from clinical trials evaluating new anticancer agents because of the potential adverse effects of new antineoplastic agents on the haemostatic system. It does appear that agents targeting the vascular endothelial growth factor receptor can be used in mild haemophilia patients without aggravation of bleeding diathesis [68].

Autologous stem cell transplantation to treat severe haemophilia may be associated with a potential for metastatic complications in patients who undergo this procedure [69]. On the other hand, interventions that target the blood coagulation cascade appear to inhibit cancer cell metastasis suggesting that congenital bleeding disorders may offer some level of protection from metastases [70,71].

In the absence of sufficient data to support the management of cancer in haemophilia patients at present, the use of patient registries and the publication of case reports will reflect the growing clinical experience and capture future epidemiological trends.

Conclusions

As the haemophilia patient population ages, a concomitant increase in age-related disorders is likely. Healthcare delivery systems will need to adapt accordingly to provide appropriate services not only for the management of bleeding, orthopaedic issues and the treatment of infectious diseases, but also to oversee the comprehensive healthcare needs of haemophilia patients. Until hard data on an ageing patient population can be generated, clinical practice guidelines are needed to improve patient care and quality of life among adult patients with chronic haemophilic arthritis, HIV and HCV infections, cardiovascular disease, cancer and other age-related conditions.

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