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Clinical challenges within the aging hemophilia population

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ABSTRACT

Older patients with hemophilia face many challenges related not only to hemophilia but also to general comorbidity associated with aging. Patients with hemophilia often have known risk factors for cardiovascular disease, such as hypertension and hepatitis C virus (HCV) infection, which may counteract any protective effects bestowed by the hypocoagulable state. Arthritis and joint disease are common and contribute to disability and pain. The high prevalence of chronic HCV infection has led to an increased risk for liver failure and hepatocellular carcinoma. Renal function and urological disorders are a concern in these patients, and issues related to sexuality are an important but often-overlooked issue. The use of routine procedures for general health maintenance in the elderly (e.g. colonoscopy) can be more complex in patients with hemophilia due to the inherent risk of bleeding, and serious disorders such as malignancy can be overlooked if signs of abnormal bleeding are attributed to hemophilia, rather than to cancer. Prospective studies are needed to address these challenges so that evidence-based guidance can be given to clinicians who treat older patients with hemophilia.

Life expectancy of patients with hemophilia has increased, thanks to improvements in disease management, including the availability of coagulation factor concentrates [1]. A nationwide analysis of life expectancy of men in the UK revealed that those with mild or moderate hemophilia have a similar life expectancy as those without hemophilia (Fig. 1) [2]. These findings highlight the advances that have been made in the management of this disease, and underscore the need for continued improvements in the management of severe hemophilia.

While the growing number of older patients with hemophilia attests to the advances in treatment that have occurred in recent decades, the increased life expectancy has created new issues not previously recognized in hemophilia care, such as cardiovascular disease (CVD) and cancer. The number of recent reviews published on the topic reflects the growing interest in dealing with the clinical challenges that arise in the management of comorbidity in older patients with hemophilia [1,3–10]. While few prospective studies have specifically addressed these challenges, data from ongoing studies are emerging that will hopefully help to guide clinicians in the management of these patients.

Joint disease

Among older men, those with hemophilia are more likely to have musculoskeletal disease compared to those without hemophilia (Fig. 2) [11]. Specifically, those with hemophilia had significantly more joint instability, flexion contractures, impaired range of motion, axial deformity, muscular atrophy, joint swelling, and chronic synovitis (Fig. 3). Arthritis and joint disease may contribute to inactivity, muscle weakness, and poor balance that can increase the risk of falls and fractures, emphasizing the importance of adequate management in older patients.

Arthritis and joint disease, arguably the most challenging chronic conditions encountered in patients with hemophilia, are also associated with the aging process, and the prevalence of these disorders increases with age [12]. Hemarthrosis can accelerate the development of arthritis and joint disease, and these disorders have been linked to an increased risk of falling – a major source of morbidity and mortality in older patients. Data from studies of younger men with hemophilia indicate that secondary prophylaxis will slow the progression of joint disease, but the role of secondary prophylaxis in older patients with established joint disease is unclear. A prospective trial (NCT00623480) is ongoing to evaluate prophylaxis in adults with established joint disease.

Orthopedic issues

Historically, men were not considered at risk of developing osteoporosis, but evidence is now emerging that indicates that it may be a common event, particularly in men with hemophilia [13–15]. Infection with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) is associated with an increased risk of osteoporosis [13,14]. Osteoporosis increases the risk of fractures, which are associated with substantial morbidity and mortality in men [16,17]. Few studies have evaluated measures that may reduce fall risk in patients with

Abbreviations: CVD, cardiovascular disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs.

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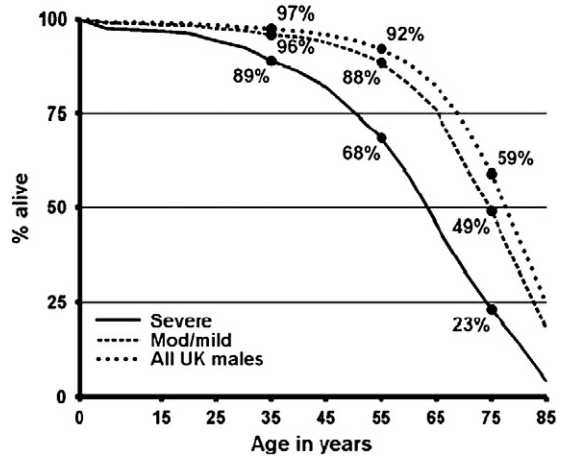

Fig. 1. Life expectancy of HIV-negative males in the UK, 1999, with severe (solid line) or mild/moderate (dashed line) hemophilia, or without hemophilia (dotted line) [2]. Reproduced with permission of The American Society of Hematology © 2007, from Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV, Darby SC et al., Blood 2007;110:815–25.

hemophilia [18], and the optimal approach to reducing fall risk in these patients has not yet been identified.

Joint replacement is an important aspect of hemophilia care, but several questions remain regarding its use in older patients, including the optimal time to initiate the procedure, the use of coagulation factor replacement therapy, and the role of thromboprophylaxis [19]. In a prospective study of 29 procedures performed without thromboprophylaxis in patients with hemophilia, no symptomatic deep-vein thrombosis or pulmonary embolism was observed, although three patients had ultrasonographic evidence of distal deep-vein thrombosis after surgery that resolved without treatment (n = 2) or after treatment with low-molecular-weight heparin (n = 1) [20]. Ongoing studies are evaluating the efficacy and safety of thromboprophylaxis in patients with hemophilia.

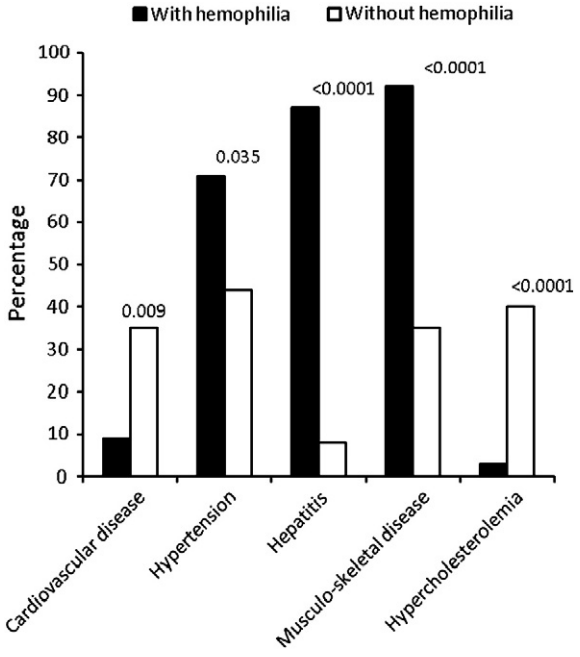

Fig. 2. Prevalence of comorbidities in men aged 65–78 years with and without hemophilia [11]. Reproduced with permission from John Wiley and Sons, Copyright © 2009, Health Status and quality of life of elderly persons with severe hemophilia born before the advent of modern replacement therapy, Siboni SM, et al., J Thromb Haemost 2009;7:780–6.

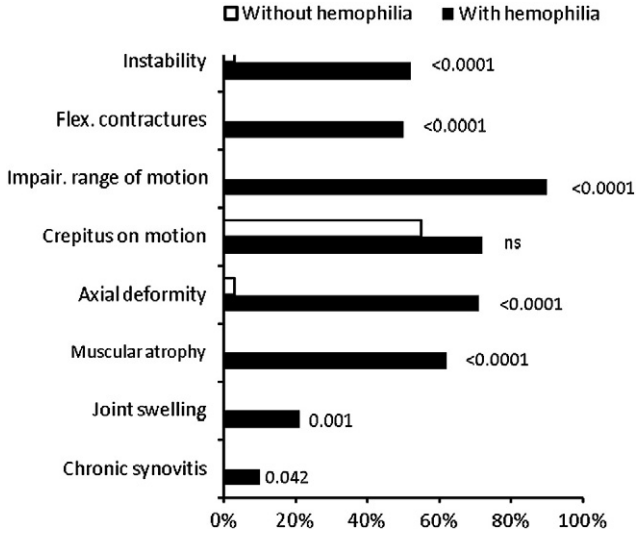

Fig. 3. Musculoskeletal impairment in men aged 65–78 years with and without hemophilia [11]. Flex., flexion; impair., impairment. Reproduced with permission from John Wiley and Sons, Copyright © 2009, Health Status and quality of life of elderly persons with severe hemophilia born before the advent of modern replacement therapy, Siboni SM, et al., J Thromb Haemost 2009;7:780–6.

Cardiovascular disease

In a survey of men aged 65–78 years conducted in Italy, the prevalence of hypertension was significantly higher in those with hemophilia than in those without hemophilia (Fig. 2) [11]. However, the prevalence of CVD and hypercholesterolemia was significantly lower in those with hemophilia; these results may have been compounded by treatment.

The prevalence of atherosclerotic disease appears to be similar in patients with and without hemophilia, but results from some studies have suggested that the risk of death due to CVD may be lower in patients with hemophilia. It has been hypothesized that the hypocoagulable state of hemophilia may exert a protective effect on thrombus formation, which can precipitate infarction, and possibly the development of atherosclerosis [5]. However, many of these studies were based on reviews of death records, which introduces the possibility of bias: if clinicians are not expecting a certain cause of death, they may be less likely to report it. Other data support a similar rate of CVD in men with hemophilia compared to the general population [21]. Importantly, men with hemophilia often have several risk factors for CVD, such as hypertension, chronic renal disease, infection with HIV or HCV, and chronic inflammation. In addition, peripheral vascular disease is increasingly recognized as a prevalent comorbidity in men with hemophilia, and its impact on outcomes warrants further investigation.

Liver disease

Infection with HCV is a major cause of liver disease, liver failure, and transplantation, making it a leading cause of death in patients with hemophilia [1]. In most cases, chronic HCV infection leads to hepatitis and some degree of fibrosis [22]. Co-infection with HIV and HCV can accelerate the progression to cirrhosis and liver failure [23]. Among older patients with hemophilia and chronic HCV infection, the prevalence of cirrhosis increases to as high as 60% [24]. Biomarkers of liver disease that can be assessed non-invasively are under investigation; this approach may prove to be particularly suitable for patients with hemophilia as it may avoid the need for liver biopsy, which currently remains the gold standard for assessing the presence and extent of liver disease and determining prognosis [25,26].

Hepatocellular carcinoma has become an increasingly important cause of death in patients with hemophilia as life expectancy has