Seminars in Hematology 53 (2016) 35–39

Contents lists available at ScienceDirect

Seminars in Hematology

journal homepage: www.elsevier.com/locate/enganabound

Aging among persons with hemophilia: contemporary concerns

Dana Angelini[a], Barbara A. Konkle[b], Suman L. Sood[a,*]

[a] Hemophilia and Coagulation Disorders Program, University of Michigan, Ann Arbor, MI, USA
[b] Bloodworks Northwest and Department of Medicine, Division of Hematology, University of Washington, Seattle, WA, USA

ARTICLE INFO

Available online 26 October 2015

Keywords:
Hemophilia
Elderly
Cardiovascular
Cancer
Arthropathy
Renal

ABSTRACT

The life expectancy of persons with hemophilia (PWH) has increased almost 10-fold over the past seven decades, largely due to access to safe factor replacement products. Concomitant with this success, however, comes the burden of aging. Older PWH are developing similar comorbidities as the general population, including increasing rates of hypertension, obesity, and diabetes, which predispose them to chronic diseases such as cardiovascular disease (CVD) and chronic kidney disease (CKD). How their coagulopathy affects the expression of these conditions remains unclear. In addition, the elderly hemophilia population must cope with chronic joint arthropathy, which provokes falls and fractures, and complications related to human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections, which greatly impact the incidence of cancer and liver disease. With a dearth of evidence-based guidelines to direct therapy, a new challenge has arisen for hematologists to optimally manage these complex age-related issues. This review will focus on common complications affecting the older hemophilia population, including joint disease, CVD, malignancy, renal insufficiency, and liver disease.

1. Introduction

Hemophilia is the most common X-linked inherited disease, affecting approximately 400,000 people worldwide [1]. With the availability of effective and safe factor concentrate, the life expectancy of persons with hemophilia (PWH) has increased substantially since the 1970s. Currently, patients with severe hemophilia not infected with human immunodeficiency virus (HIV) have a median survival into the sixth and seventh decades of life. With the use of highly active antiretroviral therapy (HAART), the survival of PWH with HIV has also improved significantly since the 1990s; 27%–39% are now surviving 20–25 years following infection [2–4]. Thus, with modern treatment, we now face a growing population of PWH with advancing age (Fig. 1). However, there is a relatively small amount of experience treating this older population and concurrent age-related diseases, raising a new challenge for hematologists. The focus of this review will be on hemophilia and age-related complications including joint disease, cardiovascular disease (CVD), malignancy, renal insufficiency, and liver disease.

2. Joint disease

Joint disease is the most common condition concerning PWH with advancing age. Prior to 1987, PWH in most countries were not treated with prophylactic factor replacement during their childhood, as this practice was not yet standard of care [5]. As a result of chronic bleeding into joints, older patients with hemophilia are living with impaired range of motion, contractures, joint instability, chronic synovitis, and muscular atrophy. These complications lead to reduced mobility and function, which increases the risk of obesity, which can lead to further strain on ailing joints. In an Italian study of men ≥ 65 years old with severe hemophilia, PWH had higher pain scores, increased risk of falls, and a sevenfold higher rate of joint replacement surgery compared to age-matched controls [6].

The knee is a frequent site of hemarthrosis and total knee replacement is the most common joint replacement performed in PWH. Ankles and elbows are other commonly affected target joints. Joint replacement surgery is best performed at a hemophilia treatment center with experienced orthopedic surgeons, nurses, social workers, physical therapists, and hematologists familiar with this patient population. Adequate peri-operative factor replacement is essential to prevent bleeding complications, and should be monitored carefully by the treating hematologist. Of note, there is no documented standard of care for venous thromboembolism prophylaxis in PWH following hip or knee replacement and decisions regarding the addition of pharmacological prophylaxis on top of promoting early ambulation are best made on a case-by-case basis.

Aside from functional impairment, PWH are also at higher risk of fractures secondary to decreased bone mineral density. This is speculated to be from chronic inflammation as well as decreased

* Corresponding author.
E-mail address: sumisood@med.umich.edu (S.L. Sood).

http://dx.doi.org/10.1053/j.seminhematol.2015.10.004
0037-1963/$/

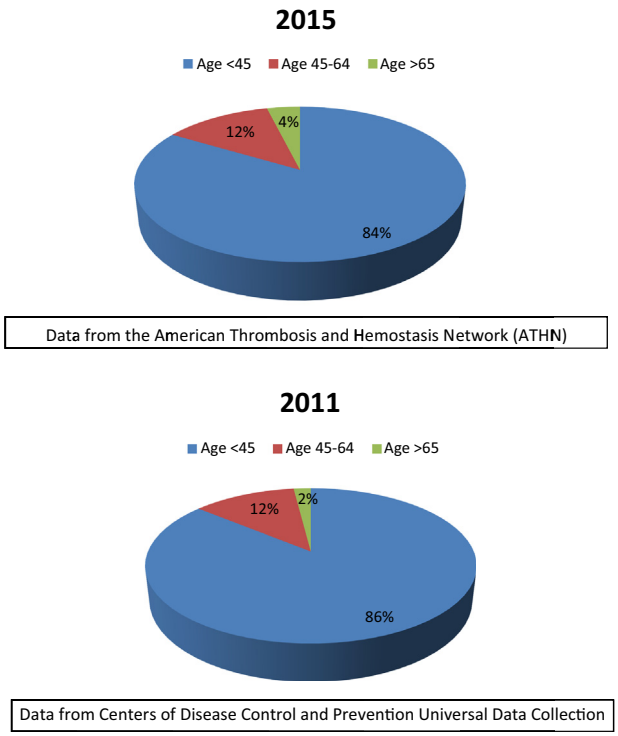

Fig. 1. Comparison of age distribution of persons with hemophilia A between 2011 and 2015.

weight bearing on affected joints. A retrospective analysis of 382 PWH reported a marked increased risk of fracture in the hemophilia population compared to controls (relative risk 10.7 (95% confidence interval [CI], 8.2–14.1, $P < .0001$). The risk of fracture corresponded with both disease severity and increasing age [7]. In an effort to mitigate the damaging effects of longstanding arthropathy, attention has turned towards preventative strategies such as exercise. Forsyth et al propose a regular exercise program incorporating strength training, balance, flexibility, and aerobics in PWH to improve joint function. In addition, such exercises can increase bone mineral density, protecting PWH from developing further osteoporosis and pathological fractures [8]. Prophylactic factor replacement should be considered prior to exercise in those with severe hemophilia.

3. Cardiovascular disease

As the hemophilia population ages, they are subject to the same risk factors to develop atherosclerotic cardiovascular disease as the general population. Moreover, the increased prevalence of hypertension (HTN), chronic kidney disease (CKD), and HIV in the hemophilia population may further promote CVD [9–11]. However, there remains controversy in the literature as to whether the lower factor (F)VIII and FIX levels that characterize hemophilia actually safeguard against the formation of ischemic events (Table 1). Some studies report a protective effect of hemophilia on the incidence of CVD, while others show an increased cardiovascular risk profile. The studies are heterogeneous and difficult to directly compare due to disparate outcomes and age ranges. In 2010, Biere-Rafi et al conducted a systematic review of arterial disease in hemophilia and found nonsignificantly reduced cardiovascular mortality in PWH compared to healthy controls (standardized mortality ratio [SMR] 0.51; 95% CI, 0.24–1.09) [12]. It is also unclear whether hemophilia protects against the development of atherosclerosis; however, the majority of available studies report a similar amount of atherosclerosis in PWH compared to controls (Table 2).

Given conflicting reports in the literature, there is clearly a need for a large prospective study to determine the risk of cardiovascular disease in hemophilia patients. Preliminary results from an ongoing US cross-sectional analysis of cardiovascular disease (The CVD in Hemophilia Study) found high rates of risk factors for CVD, including HTN (64.2%), dyslipidemia (35.1%), and renal insufficiency (29.3%) in older men ages 54–73 with moderate or severe hemophilia ($n = 148$). However, the prevalence of reported CVD was low at 10.1%, suggesting that men with hemophilia may be protected from forming pathogenic thrombi. A formal comparison with age-matched controls is planned once enrollment is complete [13].

Table 1
Standardized mortality ratio, prevalence, and main results of selected studies of cardiovascular disease in persons with hemophilia in various countries.

First author	Year published	Country	Total no. of patients	Mean age (y)	SMR (95% CI)
Triemstra [36]	1995	Netherlands	919	30	0.2 (0.0–1.1)
Soucie [24]	2000	United States	2,950	22	3.0 (1.5–5.8)
Plug [2]	2006	Netherlands	967	32	0.5 (0.2–1.1)
Darby [4]	2007	United Kingdom	6,018	NR	0.6 (0.5–0.8)
					CVD prevalence compared to general population
Kulkarni [11]	2005	United States	3,422	45–64*; ≥65	0.5; 0.7
Miesbach [20]	2009	Germany	29†	64	0.9
Siboni [6]	2009	Italy	82	65–78*	0.08 PWH *v* 0.45 controls, $P = .009$
					Main results
Biere-Rafi [37]	2011	Netherlands	300	47	Similar prevalence of CV risk factors and predicted high 10-year CVD mortality risk PWH *v* Controls: 0.12 *v* 0.07 ($P = .18$)
Ragni [33]	2011	United States	605†	NR	Similar CV risk factors and in-hospital mortality as general population: MI 14.9% *v* 18.7%, $P = .39$.
Lövdahl [38]	2012	Sweden	8581	53	Death from ischemic heart disease: PWH *v* controls 12.6% *v* 28.9%, $P < .001$
Fransen van de Putte [39]	2012	Netherlands	408†	53.7	MI PWH *v* controls: 2.5% (1.2–4.5) *v* 4.8% (4.6–4.9), $P =$ significant
Pocoski [40]	2013	United States	10,024	0–70+*	CAD and MI, PWH *v* controls: 10.7% *v* 5.8% ($P < .001$) and 0.8% *v* 0.3% ($P = .003$), respectively

SMR, standardized mortality ratio; PWH, patients with hemophilia; NR, not reported; CI, confidence interval; CVD, cardiovascular disease; CAD, coronary artery disease; MI, myocardial infarction.

* Age range.
† Hemophilia patients.