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Atherosclerotic Heart Disease: Prevalence and Risk Factors in Hospitalized Men with Hemophilia A

Margaret V. Ragni, MD, MPH[1] and **Charity G. Moore, PhD, MSPH**[2]

[1]Department of Medicine, Division of Hematology/Oncology, University of Pittsburgh, Pittsburgh PA

[2]Department of Medicine, Division of General Internal Medicine, and Center for Research on Health Care Data Center, University of Pittsburgh PA

Summary

Background—Atherosclerotic heart disease (ASHD) is a common cause of morbidity and mortality in Western society. Few studies have determined prevalence and predictors of ASHD in hemophilia (HA), a population whose survival is improving with safer blood products and effective treatments for AIDS and hepatitis C.

Objectives—The purpose of this study was to determine prevalence and factors associated with ASHD in hemophilia A patients in Pennsylvania.

Methods—The prevalence of ASHD (myocardial infarction, angina, coronary disease), cardiac catheterization, coronary angiography, co-morbidities, and in-hospital mortality were assessed on statewide ASHD discharge data, 2001–2006, from the Pennsylvania Health Care Cost Containment Council (PHC4).

Results—The prevalence of hemophilia ASHD admissions fluctuated between 6.5% and 10.5% for 2001 to 2006, p=0.62. Compared to HA without ASHD, HA with ASHD were older and more likely to be hypertensive, hyperlipidemic, and diabetic, all p<0.0001, with greater severity of illness, p=0.013. By contrast, HA and non-HA with ASHD had similar rates of hypertension, diabetes, and ICD-9 specified ischemic heart disease, including acute myocardial infarction (MI), p=0.39, old MI, p=0.47, and angina, p=0.63. Rates of catheterization and angiography, p=0.06 and p=0.07, were marginally lower, but primary circulatory system admitting diagnoses, p=0.29, were similar between HA and non-HA ASHD groups, as was length of stay, p=0.14, severity of illness, p=0.64, and in-hospital deaths, p=0.75.

Conclusions—Hemophilia patients with ASHD have similar cardiovascular risk factors, admitting diagnoses, severity of illness, and in-hospital mortality as the general population. These findings suggest cardiovascular prevention measures should be promoted in hemophilia.

Keywords

atherosclerosis; heart disease; hemophilia; prevalence; risk factors

Reprint Requests Margaret V. Ragni, MD, MPH Professor of Medicine Division Hematology/Oncology, University of Pittsburgh Medical Center Director, Hemophilia Center of Western Pennsylvania 3636 Boulevard of the Allies Pittsburgh, PA 15213-4306 Phone: 412-209-7288; Fax: 412-209-7281 ragni@dom.pitt.edu.

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Introduction

Atherosclerotic heart disease (ASHD) is the most common cause of morbidity and mortality in Western society. Among individuals with hemophilia, there is increasing interest in defining the scope of ASHD, now that their survival is approaching that of the normal population with the availability of safer clotting factor concentrates and effective treatment for blood-borne pathogens HIV and hepatitis C [1–3]. A CDC study reported that as many as 15% of hemophilic men over 60 years of age have clinical ASHD [4]. While their mortality is 2.7-fold higher than the general population, due to hepatitis C and AIDS, the mortality from ischemic heart disease is 60% lower [3,5–7]. Elevated circulating factor VIII [8], fibrinogen [9], and von Willebrand factor [10] levels are known risk factors for cardiovascular disease, but whether low factor VIII or IX, i.e. hypocoagulability, protects against ASHD remains an area of debate. In a recent case-control study we found that risk factors for ischemic heart disease (hypertension, smoking, diabetes, hyperlipidemia) and degree of intraluminal coronary stenosis at autopsy in hemophilic men are similar to those in the general population [11]. This suggests that while risk for cardiovascular disease is similar, the risk for cardiovascular mortality is lower in individuals with hemophilia than the general population, despite improving lifespan, and this may be related to hypocoagulability [11,12]. Few data, however, exist on the prevalence and predictors of ASHD in hospitalized hemophilia patients as compared with the general population. While some studies describe a lower frequency of lipid elevation in those with hemophilia than controls [13], others studies report no difference [14,15], suggesting differences in age, viral infection, obesity, or other confounders between these groups [16]. We, therefore, reviewed statewide inpatient ASHD discharge data for ASHD from the Pennsylvania Health Care Cost Containment Council (PHC4) to determine the prevalence and characteristics of ASHD in hospitalized hemophilia patients in Pennsylvania.

Methods

De-identified discharge data for the five-year period 2001–2006 were obtained from the Pennsylvania Health Care Cost Containment Council (PHC4). This independent agency collects inpatient hospital discharge data and outpatient procedure records from hospitals and ambulatory surgery centers in the state of Pennsylvania to monitor health care cost [17]. Data for analysis were limited to Pennsylvania residents hospitalized between 2001 and 2006, excluding female patients. Discharges were analyzed by age, race, year, severity of illness, length of stay, and vital status including in-hospital deaths [17,18]. Coronary disease data were classified by diagnostic ICD-9 codes [19] for atherosclerotic heart disease (ICD-9 414), myocardial infarction (ICD-9 412), angina (ICD-9 413), and other ischemic heart disease (ICD-9 411). Cardiac diagnostic procedure codes were classified by procedure codes, including cardiac catheterization, EKG, angiography, and nuclear procedures. Co-morbidities were also assessed, including hypertension (ICD-9 401–405), hyperlipidemia (ICD-9 272.4); diabetes (ICD-9 250), obesity (ICD-9 278), and HIV (ICD-9 042). Primary admission diagnoses were classified as circulatory system (ICD-9 390–460), blood-forming organs (ICD-9 280–290), respiratory system (ICD-9 460–520), digestive system (ICD-9 520–580), and injury/trauma (ICD-9 800–999). Three groups of hospitalized patients were identified for comparisons: 1) individuals with hemophilia A and ASHD; 2) those with hemophilia A and no ASHD; and 3) individuals without hemophilia A but with ASHD, based on the presence or absence of these two diseases in the primary or secondary diagnoses (admissions categorization). The study was approved by the University of Pittsburgh Institutional Review Board (IRB) by exempt review.

Analysis

The annual prevalence of ASHD among hemophilia A admissions was estimated by dividing the number of admissions with ASHD and hemophilia A diagnosis by the total number of hemophilia admissions per year. Primary comparisons for analyses were carried out 1) to determine how hemophilia patients with ASHD compare to their non-hemophilia counterparts with ASHD; and 2) to determine how hemophilia patients with ASHD compared to their hemophilia counterparts without ASHD. We limited analysis to the first admission per patient once the admission categorization was determined to decrease the influence of multiple correlated admissions from the same patient on group comparisons. We compared continuous data (e.g. age, length of stay) was by Student t-test, and categorical data (e.g.race, co-morbidities, procedures) using Chi-square tests.

Results

Prevalence of ASHD among hospitalizations in men with hemophilia A

The prevalence of ASHD admissions among individuals with hemophilia (HA) fluctuated between 6.5% and 10.5% during the time period 2001 to 2006, p=0.62 (Figure 1). The age-specific prevalence of ASHD was consistently higher in older-age compared to younger-age categories, for all admissions and by year, p<0.0001, with 1.28% (n=941) for those ≤50 years, 10.9% (n=156) for 51–64 years, 33.6% (n=110) for 65–74 years, and 31.8% (n=173) for ≥75 years of age.

Comparison of Hemophilia A patients with ASHD and without ASHD

As compared with hemophilia inpatients without ASHD, hemophilia inpatients with ASHD were older, 73 vs. 39 yr, and more likely to have hypertension, 52.7% vs. 21.1%, hyperlipidemia, 9.5% vs. 1.3%, and diabetes, 28.4% vs. 9.4%, all p<0.0001. Hemophilia inpatients with ASHD were less likely to be admitted for injury or trauma, p<0.0001, but had a greater severity of illness than those without ASHD, p=0.013. The two groups had a similar length of stay, 5.9 vs. 5.0 days, p=0.30, and a similar proportion of in-hospital deaths, 4.1% vs. 2.3%, p=0.41.

Comparison of ASHD patients with hemophilia and without hemophilia

Hospitalized hemophilic ASHD patients were as likely as non-hemophilic ASHD patients to be hypertensive, 52.7% vs. 56.2%, p=0.54, diabetic, 28.4% vs. 27.1%, p=0.80, and obese, 4.1% vs. 4.6%, p=1.00. Hyperlipidemia was significantly less common in hemophilic than nonhemophilic ASHD inpatients, 9.5% vs. 22.9%, p=0.006, even after adjustment for age, p=0.007, although no differences were noted in rates of obesity between the groups, p=1.00. Unfortunately, neither cholesterol levels nor body-mass index measures were available to quantify these findings. As expected, HIV infection was more common among ASHD inpatients with hemophilia than in those without hemophilia, 2.7% vs. 0.1%, p=0.002; as was HCV infection, 12.2% vs. 0.6%, p<0.0001. Hemophilic ASHD inpatients were just as likely as their non-hemophilic counterparts to have circulatory system disease as a primary admission diagnosis, 52.7% vs. 58.7%, p=0.29.

These two groups also had similar rates of ICD-9 specified ischemic heart disease, including acute myocardial infarction (MI), p=0.39, old MI, p=0.47, and angina, p=0.63. Hemophilic ASHD inpatients underwent somewhat fewer coronary catheterization procedures than nonhemophilic ASHD inpatients, 16.2% vs. 25.8%, and somewhat fewer coronary angiography procedures, 16.2% vs. 25.5%, p=0.06 and p=0.07, respectively.

Although length of stay was longer among hemophilic than non-hemophilic patients with ASHD, 5.9 vs 4.9 days, this did not reach significance, p=0.13. There were also no

differences in severity of illness scores, p=0.64, or in-hospital deaths, 4.1% vs. 3.6%, p=0.75, between groups.

Discussion

As the hemophilia population is now aging, a number of studies have established that while cardiovascular mortality is three times more common as a cause of death [20], cardiovascular disease [3,6,7,12,21,22], pathologic coronary artery atherosclerosis [11], and endothelial dysfunction [14] do not differ between individuals with hemophilia and the general population. Further, the prevalence of ASHD is not uncommon in older individuals in normal, nonhemophilia groups. However, there is controversy regarding whether those with hemophilia have similar cardiovascular risk factors to those in the general population. Some of the difficulties with studies to date include small cohort size, few cardiovascular events, and differing age, decade of study, and proportion HIV infected or on antiretroviral therapy.

This study utilized hospital discharge data to establish that, as compared with non-hemophilic men with ASHD, hemophilic men with ASHD have *similar* cardiovascular risk factors with the exception of hyperlipidemia, and they also have *similar* primary admitting (non-hemophilic) diagnoses. Further, they have *similar* cardiovascular ICD-9 codes for myocardial infarction and angina pectoris, a *similar* severity of illness, and a *similar* proportion who undergo cardiovascular diagnostic procedures. It is of note that the trend to fewer undergoing coronary angiography, although not significant, is possibly related to fear of bleeding, not only by persons with hemophilia, but by the cardiologists caring for them.

The findings of this study suggest that cardiovascular procedures should be part of standard medical care for individuals with hemophilia, just as for the general population. There are, however, important caveats to consider in this approach. Anticoagulation or anti-platelet therapy, whether for myocardial infarction or surgical procedures, e.g. coronary stent placement, may increase the risk of life-threatening bleeding in the individual with hemophilia. Further, the risk of bleeding may be even greater in the presence of other concomitant coagulation defects, e.g. thrombocytopenia or Vitamin K deficiency, not uncommon in hemophilic men with chronic hepatitis C liver disease. Thus, before initiating anticoagulation or platelet inhibitor therapy in the individual with hemophilia, careful coagulation assessment before and during anticoagulation or anti-platelet therapy is critical to avoid unforeseen bleeding. It is of note that no safety recommendations or evidence-based guidelines exist to guide anticoagulation or anti-platelet therapy in hemophilic men. This is, in part, because potential bleeding risk excludes hemophilic men them from participation in cardiovascular prevention trials. In the absence of evidence, wide-ranging approaches to anticoagulation and anti-platelet therapy for cardiovascular disease and/or procedures have been proposed, including short-term anticoagulation anti-platelet therapy only with concomitant factor infusion, low dose anticoagulation or anti-platelet therapy, or avoidance of such agents altogether [23]. The lack of hemophilia-specific guidelines for anticoagulation management of ischemic cardiovascular disease suggests the need for prospective clinical trials, which would likely require international collaboration for sufficient sample size to achieve significant findings.

There are several limitations of this study. First, the use of a hospital discharge database may miss healthier outpatients not requiring admission; however, traditionally patients with acute myocardial infarction and angina pectoris, the ICD-9 codes we reviewed, are hospitalized, and, thus, we believe few potential subjects were missed. Further, an advantage of an inpatient database is the availability of severity of illness and in-hospital mortality data, not previously reported in hemophilic men. Secondly, because these are administrative data

collected for another purpose, it is not possible to verify that all patients with an ICD-9 for hemophilia actually had hemophilia, nor is it possible to establish hemophilia severity, although previous studies suggest no difference in ASHD risk by hemophilia severity [11]. Further, these data do not include clinical history of smoking, laboratory values,, e.g. lipid levels, or treatment medications for hypertension or hyperlipidemia, which may result in identification of fewer individuals with hyperlipidemia or at risk for cardiovascular disease. Thirdly, these data are limited to the state of Pennsylvania which, although unlikely, may not be representative of the nation and miss geographic differences. Fourthly, as expected, HIV infection was more common among ASHD inpatients with hemophilia than in those without hemophilia, yet the prevalence was low, in only 2.7% of patients with hemophilia. The reason for this is not known, but it is possible this reflects the advanced age of the patient population, and/or limitations of hospital discharge coding.

To summarize, the presence of atherosclerotic heart disease among adult men with hemophilia is not rare (6–10% of admissions). Cardiovascular risk factors, severity of illness and in-hospital mortality are similar in hemophilia men with ASHD compared to the general population of men with ASHD. These findings are consistent with the previous demonstration that pathologic coronary atherosclerosis [11] and endothelial dysfunction [14] in those with hemophilia are similar to the general population, and underscore the importance of a cardiovascular risk prevention strategy in adults with hemophilia, similar to that in the general population. Such a strategy will require ongoing clinical studies to define the safety of anticoagulation and anti-platelet therapy in this group.

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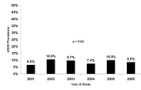

Figure 1. Prevalence of ASHD among Hemophilia A Inpatients 2001–2006

The bar graph illustrates the prevalence of all ASHD admissions among admissions/ hospitalizations in men with hemophilia A in the state of Pennsylvania. The mean annual percent is indicated above each bar.

Table 1

Characteristics of Hemophilia and ASHD, Non-ASHD, and Non-Hemophilic ASHD Admissions in Pennsylvania

	Group 1 Hemophilia ASHD	Group 2 Hemophilia No ASHD	Group 3 Non-Hemophilia ASHD	p value Group 1 vs. Group 2	p value Group 1 vs. Group 3
No. of Admissions	N = 196	N = 1,623	N = 2,270,318		
No. of Patients	N = 74	N = 531	N = 483,782		
Age (median, years)	73	39	70	p<0.0001	p=0.889
Race Non Hispanic white	89.6%	77.9%	90.9%	p=0.132	p=0.703
Non Hispanic Black	9.0%	14.4%	6.4%		
Hispanic	1.5%	6.1%	1.6%		
Non-Hispanic Other	0.0%	1.6%	1.1%		
Risk Factors					
Hypertension	52.7%	21.1%	56.2%	p<0.0001	p=0.543
Hyperlipidemia	9.5%	1.3%	22.9%	p<0.0001	p=0.006
Diabetes	28.4%	9.4%	27.1%	p<0.0001	p=0.805
Obesity	4.1%	1.5%	4.6%	p=0.141	p=1.000
HIV Infection	2.7%	5.6%	0.1%	p=0.409	p=0.002
HCV Infection	12.2%	24.3%	0.6%	p=0.0198	p<0.0001
Altas Severity of Illness					
None	14.8%	34.1%	18.8%	p=0.013	p=0.637
Minimal	42.6%	38.7%	40.2%		
Moderate	26.2%	17.0%	28.2%		
Severe	16.4%	8.8%	11.7%		
Maximal	0.0%	1.4%	1.1%		
Atlas Severity of Illness, Dichotomized					
None/Minimal/Moderate	83.6%	89.8%	87.2%	p=0.151	p=0.405
Severe/Maximal	16.4%	10.2%	12.8%		
Primary Admission Diagnosis					
Circulatory System	52.7%	7.2%	58.7%	p<0.0001	p=0.293
Blood-Forming Organs	14.9%	18.6%	0.5%	p=0.430	p<0.0001
Respiratory System	1.4%	6.0%	7.0%	p=0.165	p=0.064
Digestive System	10.8%	11.9%	5.8%	p=0.792	p=0.063

	Group 1 Hemophilia ASHD	Group 2 Hemophilia No ASHD	Group 3 Non-Hemophilia ASHD	p value Group 1 vs. Group 2	p value Group 1 vs. Group 3
Injury, Trauma	4.1%	18.3%	4.4%	p=0.001	p=1.000
ICD-9 Codes					
ICD-9 410 (AMI*)	14.9%	0.0%	18.7%	-	p=0.393
ICD-9 411 (Other IHD†)	16.2%	0.0%	11.6%	-	p=0.214
ICD-9 412 (Old MI)	13.5%	0.0%	16.6%	-	p=0.470
ICD-9 413 (Angina pectoris)	4.1%	0.0%	6.0%	-	p=0.629
ICD-9 414 (ASHD‡, other)	85.1%	0.0%	86.7%	-	p=0.688
Cardiac Diagnostic Procedures					
Cardiac catheterization	16.2%	0.4%	25.8%	-	p=0.060
Cardiac echocardiogram	5.4%	1.1%	3.4%	-	p=0.325
Coronary angiography	16.2%	0.6%	25.5%	-	p=0.067
Transesophageal echogram	5.4%	0.9%	3.4%	-	p=0.323
Intravascular Imaging	0.0%	0.0%	0.1%	-	p=1.000
Length of Stay (mean days)	5.9	5.0	4.9	p=0.300	p=0.135
Discharged on Admit Day	4.1%	2.1%	1.8%	p=0.397	p=0.147
In-Hospital Death	4.1%	2.3%	3.6%	p=0.412	p=0.752
Died on Admit Day	33.3%	0.0%	19.5%	p=0.214	p=0.478

*AMI is acute myocardial infarction.

†IHD is ischemic heart disease.

‡ASHD is atherosclerotic heart disease.

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