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Haemophilia A Carriers Experience Reduced Health-Related Quality of Life

Leslie Gilbert, MD¹, Allison Paroskie, MD MSCI¹, David Gailani, MD¹, Michael R. Debaun, MD MPH¹, and Robert F. Sidonio Jr., MD MSc²

¹Vanderbilt University, Nashville, TN

²Children's Healthcare of Atlanta/Emory University, Atlanta, GA

Abstract

Introduction—Haemophilia A is an X-linked recessive bleeding disorder that primarily affects males. Emerging data support evidence for increased bleeding in female haemophilia A carriers despite factor VIII activity within the normal range.

Aim—Data regarding the effect of increased bleeding on health-related quality of life (HR-QOL) in haemophilia A carriers is sparse. We tested the hypothesis that haemophilia A carriers have reduced HR-QOL related to bleeding symptoms.

Methods—We conducted a cross-sectional study at Vanderbilt University. Case subjects were obligate or genetically verified haemophilia A carriers age 18 to 60 years. Control subjects were mothers of children with cancer who receive care at the Vanderbilt pediatric hematology-oncology clinic. Trained interviewers administered the Rand 36-Item Health Survey 1.0, a validated questionnaire evaluating eight health concepts that may affect HR-QOL, to each study participant. Mann-Whitney U tests were used to compare median scores for the eight health domains between the case and control groups.

Result—Forty-two haemophilia A carriers and 36 control subjects were included in analyses. Haemophilia A carriers had significantly lower median scores for the domains of “Pain” (73.75 versus 90; $p=0.02$) and “General health” (75 versus 85; $p=0.01$) compared to control subjects.

Conclusion—Haemophilia A carriers in our study demonstrated significantly lower median scores on the Rand 36-item Health Survey 1.0 in the domains of “Pain” and “General Health” compared to women in the control group. Our findings highlight the need for further investigation of the effect of bleeding on HR-QOL in this population.

Correspondence Robert F. Sidonio Jr. MD, MSc; Division of Pediatric Hematology-Oncology, Department of Pediatrics; Emory University School of Medicine; 1760 Haygood Drive, Health Sciences Research Building, Suite 340, Atlanta GA 30322; 404-727-2846 (office) robert.sidonio.jr@emory.edu.

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Keywords

Haemophilia carrier; health-related quality of life; Rand 36-item health survey 1.0; short form 36 (SF-36); women with bleeding disorders; factor VIII deficiency

Introduction

Haemophilia A is an X-linked recessive disorder caused by mutations affecting the gene for coagulation factor VIII (FVIII). Deficiency of plasma FVIII activity leads to a hemorrhagic condition characterized by a propensity to bleed into joints (hemarthrosis). Mounting evidence supports the concept that females who are heterozygous for a causative mutation, known as haemophilia A carriers, may also have significant bleeding symptoms. Plug et al demonstrated increased reported bleeding symptoms in haemophilia carriers with FVIII activity within the low normal range (0.41 to 0.6 IU/ml). Additionally, the data suggested that prolonged bleeding in haemophilia carriers results in increased medical intervention and morbidity despite normal FVIII activity [1].

Individuals with inherited bleeding disorders often have reduced health-related quality of life (HR-QOL). For example, males with haemophilia have decreased HR-QOL compared with the general population. Utilizing the Dutch Short Form-36 (SF-36) questionnaire, Fischer et al demonstrated that males with moderate to severe haemophilia have a significant decrease in the Physical Health Component Summary Score that correlates with their degree of arthropathy [2]. Only two studies have evaluated HR-QOL in haemophilia carriers. In a study of fifteen females heterozygous for a mutation of either the gene for FVIII or factor IX (FIX), and with plasma FVIII or FIX activity in the moderate to severe range (0.05 IU/ml), subjects with recurrent bleeding in one specific joint had significantly lower Physical Health Component Summary Scores on the SF-36 questionnaire compared to subjects without bleeding into a target joint [3]. Furthermore, Kadir et al administered a questionnaire via postal survey to women with inherited bleeding disorders, including seventeen haemophilia A carriers and seven haemophilia B carriers, specifically looking at the effect of menstruation on quality of life. They found that women with inherited bleeding disorders experience poorer HR-QOL related to menorrhagia and dysmenorrhea [4]. Thus, data on HR-QOL in haemophilia carriers is sparse and limited to studies with small sample sizes. However, the information that is available suggests that abnormal bleeding is an underappreciated problem in haemophilia carriers. To further elucidate the effect of haemophilia A carrier status on HR-QOL, we tested the hypothesis that haemophilia A carriers will have reduced HR-QOL related to reported bleeding symptoms.

Materials and Methods

We conducted a cross-sectional study after obtaining Institutional Review Board approval at Vanderbilt University in Nashville, Tennessee. Biological mothers or aunts of males with haemophilia A and haemophilia A carriers who receive care at Vanderbilt University were approached for enrollment. Genetically verified or obligate haemophilia A carriers age 18 to 60 years were eligible for inclusion as cases. Obligate haemophilia A carriers were defined as daughters of males with haemophilia A, mothers of two or more sons with haemophilia

A, or mothers of one son with haemophilia A who also had another male relative with haemophilia A. Potential haemophilia A carriers were identified through an electronic registry of known males with haemophilia A and were contacted directly at clinic visits or via telephone. Control subjects were mothers of patients undergoing treatment for cancer in the pediatric hematology-oncology clinic at Monroe Carell Jr. Children's Hospital at Vanderbilt. Potential control participants were identified from a list of current pediatric oncology patients and were contacted directly at their child's clinic visit or during a hospitalization. Exclusion criteria included diagnosis of another bleeding disorder, inherited or acquired thrombophilia, pregnancy, or autoimmune disorder. Informed consent was obtained prior to any study procedures taking place.

Demographic data including age, ethnicity, level of education, employment status, and health insurance status were obtained for each study participant. Additionally, height and weight were obtained for each study participant. Laboratory assessment to evaluate for other coagulopathies included a complete blood count, prothrombin time (PT), activated partial thromboplastin time (aPTT), FVIII activity (FVIII:C), von Willebrand factor antigen, ristocetin cofactor activity, and platelet function analyser-100™ study. The presence of acquired and inherited thrombophilia was evaluated using a standard hypercoagulation panel that included protein C activity, protein S activity, antithrombin activity, activated protein C resistance screen with a reflex factor V Leiden mutation analysis by polymerase chain reaction (PCR), prothrombin G20210A mutation analysis by PCR, anti-cardiolipin IgG, IgM, and IgA, beta-2-glycoprotein IgG and IgA, dilute Russell viper venom time, and lupus anticoagulant ST-LA. Tositto bleeding scores [5] and evaluation of menstrual bleeding with pictorial blood assessment charts [6] were collected on all participants. As some participants were no longer experiencing menstrual cycles due to menopause, hysterectomy or hormonal control of menses, each participant completed a pictorial blood assessment chart on her current menstrual cycle and on what she recalled as her worst menstrual cycle. The pictorial blood assessment chart score for the worst menstrual cycle was used in analyses.

Trained interviewers administered the Rand 36-item Health Survey 1.0, a validated questionnaire evaluating eight health concepts that may affect quality of life, to all study participants. Questionnaire results were evaluated with a standardized scoring system yielding separate scores for the following eight health domains: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well being, social functioning, pain, and general health. Scores for each domain range from 0 to 100 with a lower score indicating poorer HR-QOL [7, 8]. Mann-Whitney U tests were used to compare the median scores for the eight health domains obtained from the Rand 36-item Health Survey 1.0 as well as the median Tositto bleeding scores, median pictorial blood assessment chart scores, median plasma FVIII:C, and median von Willebrand factor antigen of haemophilia A carriers with those of the control group. Analyses were performed using IBM SPSS Statistics version 22 software.

Results

Eighty subjects consented to participate in this study. Three haemophilia A carriers and ten potential control subjects declined to participate in the study. One haemophilia A carrier was

excluded due to a concomitant diagnosis of von Willebrand disease, and one control subject was excluded due to heterozygosity for factor V Leiden mutation. One patient from each arm failed to complete the Rand 36-item Health Survey 1.0 leaving 42 haemophilia A carriers and 36 control subjects in the final analysis. Baseline characteristics are reported in table 1. Regarding the affected relatives of haemophilia A carriers in our cohort, 28 (67%) had severe haemophilia A, 5 (12%) had moderate haemophilia A, and 9 (21%) had mild haemophilia A. The median plasma FVIII:C was significantly lower in haemophilia A carriers than in controls (0.79 IU/ml versus 1.38 IU/ml; $p<0.001$). One haemophilia A carrier had plasma FVIII:C outside of the normal range (0.37 IU/ml), while all other study participants had plasma FVIII:C within the normal range (FVIII 0.5 IU/ml). Additionally, the interquartile range of plasma FVIII:C for haemophilia A carriers was 47 (58, 105) versus an interquartile range of 67 (109.5, 176.5) for control subjects. The median aPTT for haemophilia A carriers was higher than the median aPTT for the control population; however, it remained within normal limits. There was no significant difference between the haemophilia A carrier and control populations for the remaining baseline laboratory tests.

Haemophilia A carriers reported more severe bleeding symptoms than control subjects. The median Tositto bleeding score of haemophilia A carriers was significantly higher than for women in the control arm (5 versus 1; $p<0.001$). Also, haemophilia A carriers reported greater menstrual blood loss than controls as indicated by a significantly higher median pictorial blood assessment chart score (423 versus 182.5; $p=0.01$).

Haemophilia A carriers had significantly lower scores in the “Pain” and “General Health” domains of the Rand 36-item Health Survey 1.0 than controls. Haemophilia A carriers had a median “Pain” score of 73.75 compared to a median score of 90 for control subjects ($p=0.02$). For the “General health” domain, haemophilia A carriers had a median score of 75 compared to a median score of 85 for controls ($p=0.01$). When the study participant with FVIII:C below the lower limit of the normal range was excluded from analysis, the statistical significance for both domains remained.

Additionally, haemophilia A carriers exhibited a trend toward lower scores in the domain of “Role Limitations due to Physical Health” although the difference did not reach statistical significance in our cohort ($p=0.07$). In “Role Limitations due to Physical Health”, 32 of 36 (89%) control subjects scored 100 compared with 31 of 42 (74%) haemophilia A carriers. Furthermore, 10 of 42 (24%) haemophilia A carriers demonstrated scores ≤ 25 compared with only 1 of 36 (3%) control subjects.

The Tositto bleeding score and pictorial blood assessment chart scores were negatively correlated with the Rand 36-Item Health Survey domain scores based on the Spearman's rho test. Among the haemophilia A carrier population, the Tositto bleeding score was negatively correlated with the Pain ($r^2=0.1$, $p=0.04$), Physical Functioning ($r^2=0.21$, $p=0.003$), and Energy/Fatigue ($r^2=0.11$, $p=0.03$) domains. The pictorial blood assessment chart score was negatively correlated with the Physical Functioning ($r^2=0.14$, $p=0.02$) and Energy/Fatigue ($r^2=0.1$, $p=0.04$) domains. Among the control population, the pictorial blood assessment chart score was negatively correlated with the Emotional Well-Being domain ($r^2=0.14$, $p=0.03$). No other statistically significant correlations were identified.

Discussion

Data on quality of life for haemophilia carriers are limited. Two previous studies in this population have demonstrated poorer HR-QOL in haemophilia carriers; however, the studies were limited to symptomatic carriers with moderate or severe phenotypes or focused on HR-QOL as it relates to heavy menstrual bleeding [3, 4]. To our knowledge, this study is the first to evaluate HR-QOL in haemophilia A carriers with normal FVIII:C. Our analysis indicates that haemophilia A carriers tend to have poorer HR-QOL than women who are not haemophilia A carriers, particularly in the areas of pain and general health.

Despite the fact that all but one subject in our cohort had plasma FVIII:C within the normal range (within two standard deviations of the population mean), haemophilia A carriers reported increased bleeding symptoms as measured by the Tosetto bleeding score and the pictorial blood assessment chart compared to the control population. The Tosetto bleeding score can range from -3 to 45 with a higher score indicating increased bleeding symptoms, and a Tosetto bleeding score greater than three is indicative of abnormal bleeding [5, 9]. The median Tosetto bleeding score of five for our haemophilia A carrier cohort indicates increased bleeding in this population when compared to a median score of one in the control population. Pictorial blood assessment chart scores of greater than 100 are indicative of heavy menstrual bleeding [6], and our haemophilia A carrier cohort had a median pictorial blood assessment chart score of 423.

Although the median plasma FVIII:C of the haemophilia A carrier cohort was within the normal range, it was significantly lower than the median plasma FVIII:C of the control population. Additionally, the plasma FVIII:C of haemophilia A carriers was disproportionately skewed toward lower levels when compared with control subjects. Specifically, 25% of haemophilia A carriers had plasma FVIII:C at or below 0.58 IU/ml; whereas, the lowest plasma FVIII:C noted among control subjects was 0.68 IU/ml. We evaluated FVIII:C when participants were perceived to be at a steady state as levels can be falsely elevated in the setting of inflammation; however, FVIII:C may be even lower if re-tested. These findings suggest that patients with low-normal plasma FVIII:C in the setting of a heterozygous FVIII gene mutation have an increased bleeding tendency. Although a normal range has been established, FVIII:C could be viewed as a continuum with an increased bleeding phenotype starting within the low-normal range and worsening as plasma FVIII:C extends further into the abnormal range. A similar relationship has been described between von Willebrand factor antigen and bleeding [10].

A propensity for heavy menstrual bleeding may explain, at least in part, the decreased HR-QOL in haemophilia A carriers. In a systematic review of five studies involving 1171 females with inherited bleeding disorders, women with menorrhagia had poorer HR-QOL in all eight domains of the SF-36 questionnaire than woman without menorrhagia [11]. Haemophilia A carriers in our study had significantly higher pictorial blood assessment chart scores, a semi-quantitative assessment of menstrual blood loss, compared to women in the control group. Our findings are in line with previous studies reporting women with inherited bleeding disorders experience increased menstrual blood loss as measured by the pictorial blood assessment chart [12].

Underlying joint damage from subclinical joint bleeding may contribute to lower HR-QOL in haemophilia A carriers. Our group recently published data on nine haemophilia A carriers with normal plasma FVIII:C who demonstrated decreased joint range of motion, soft tissue and osteochondral changes on joint MRI, and International Prophylaxis Study Group (IPSG) scores consistent with previous joint bleeding and subsequent joint damage [13]. In males with haemophilia, quality of life is correlated with degree of hemarthropathy [2]. Joint pain from previous episodes of subclinical joint bleeding may contribute to decreased HR-QOL in haemophilia A carriers, specifically to decreased scores in the “Pain” domain of the Rand 36-Item Health Survey 1.0.

Women in our control group demonstrated significantly lower scores in the “Role Limitations due to Emotional Problems” domain of the Rand 36-item Health Survey 1.0. Given that our control population consists of mothers of children with cancer, this finding is not unexpected and likely the result of the emotional stress of having a child with a life-threatening illness. We chose this control population as they are from the same reference population as our cases. As with our haemophilia carrier population, these women are mothers of chronically ill children frequently seen in the Vanderbilt pediatric hematology-oncology clinic, who have an increased bleeding tendency and temporary indwelling central venous access devices.

Reporting bias is a possible limitation of our study, as with most studies based on questionnaires. Haemophilia carriers who experience more bleeding symptoms may have been more likely to agree to participate than those who are asymptomatic. To counteract this possibility, we compiled a comprehensive list of individuals who met inclusion criteria and contacted them in alphabetical order to offer enrollment in this study. Another potential limitation was the lack of a disease specific quality of life assessment; however, the SF-36 is validated for use in many disease and non-disease states [8].

Our ongoing investigation of the bleeding phenotype of haemophilia A carriers has prompted us to consider current medical management strategies for prevention of bleeding in haemophilia A carriers. Symptomatic haemophilia A carriers with FVIII:C in the range of mild to moderate haemophilia should be managed according to the guidelines established for males with haemophilia. The dilemma lies in determining the optimal management of symptomatic haemophilia A carriers with “normal FVIII:C” (>0.4 to 0.5 IU/ml) and a high pictorial blood assessment chart score and bleeding score. At this time, there is not sufficient data to support the use of factor replacement products or synthetic desmopressin; however, this is under further investigation.

Conclusion

In conclusion, haemophilia A carriers experience poorer HR-QOL as reflected by significantly lower median scores on the “Pain” and “General Health” domain assessments of the Rand 36-Item Health Survey 1.0. The haemophilia A carriers in this cohort also reported significantly higher Tositto bleeding scores and pictorial blood assessment chart scores supporting the premise that low-normal plasma FVIII:C in these individuals predisposes to increased bleeding. Our findings highlight the need for further investigation

of bleeding in haemophilia carriers and the impact of bleeding on HR-QOL in this population.

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Table 1

Baseline Characteristics

	Haemophilia A Carrier (n=42) (Median (range))	Control (n=36) (Median (range))	Mann-Whitney U Test p-value
Age (years)	37 (24 to 59)	36 (25 to 54)	0.87
BMI * (kg/m ²)	26.8 (18.9 to 42.5)	27.1 (19.7 to 34.7)	0.49
Factor VIII Activity (IU/ml)	79 (37 to 195)	138 (68 to 242)	<0.001
Tosetto Bleeding Score **	5 (0 to 17)	1 (-2 to 8)	<0.001
PBAC Score [§]	423 (29 to 2080)	182.5 (10 to 1800)	0.01
Von Willebrand Antigen (%)	102 (47 to 212)	94 (52 to 165)	0.34

* Information for BMI was unavailable for 13 participants (4 cases, 9 controls).

** The Tosetto bleeding score is calculated from a questionnaire assessing bleeding in 12 separate categories, each graded from -1 to 4 with the range of grade depending on the category. Total scores can range from -3 to 45. A higher score indicates increased bleeding symptoms. A bleeding score of <3 indicates an abnormal bleeding history [5, 9].

[§] The Pictorial Blood Assessment Chart (PBAC) is a tool used to assess menstrual blood loss based on patient report of the degree of sanitary pad/tampon soiling by blood. A PBAC score >100 indicates menorrhagia [6].

Table 2

Health Related Quality of Life by Rand 36-Item Health Survey 1.0*

Health Score	Haemophilia A Carrier Score (n=42) (Median (range))	Control Score (n=36) (Median (range))	Mann-Whitney U Test (p-value)
Physical Functioning	100 (0–100)	100 (35–100)	0.19
Role Limitations due to Physical Health	100 (0–100)	100 (0–100)	0.07
Role Limitations due to Emotional Problems [§]	100 (0–100)	100 (0–100)**	0.02
Energy/Fatigue	65 (15–85)	50 (15–100)	0.26
Emotional Well-Being	86 (52–100)	84 (12–100)	0.13
Social Functioning	100 (45–100)	100 (0–100)	0.24
Pain	73.75 (0–100)**	90 (22.5–100)	0.02
General Health	75 (25–100)**	85 (20–100)	0.01

* The Rand 36-item Health Survey 1.0 is a validated 36-item questionnaire measuring health related quality of life in 8 health domains. Scores range from 0 to 100 for each domain, and a lower score indicates poorer health related quality of life [7, 8].

** Indicates a Health Score that is significantly lower ($p < 0.05$)

[§] In the domain of Role Limitations due to Emotional Problems, the median score for both groups is 100; however, due to skewness in the data, there is a statistically significant difference between the groups. The proportion of women reporting a score of zero for this domain was higher in the control group (7 of 36 (19%) control subjects versus 2 of 42 (5%) haemophilia A carriers). The proportion of women reporting a score of 100 was higher in the haemophilia A carrier cohort (36 of 42 (86%) haemophilia A carriers versus 22 of 36 (61%) control subjects).