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Both Hemophilia Health Care Providers and Hemophilia A Carriers Report that Carriers have Excessive Bleeding

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Abstract

Introduction—Hemophilia A, the result of reduced factor VIII (FVIII) activity, is an X-linked recessive bleeding disorder. Previous reports of Hemophilia A carriers suggest an increased bleeding tendency. Our objective was to determine the attitudes and understanding of the Hemophilia A carrier bleeding phenotype, and opinions regarding timing of carrier testing from the perspective of both medical providers and affected patients. Data from this survey was used as preliminary data for an ongoing prospective study.

Material and Methods—An electronic survey was distributed to physicians and nurses employed at Hemophilia Treatment Centers (HTC), and Hemophilia A carriers who were members of Hemophilia Federation of America. Questions focused on the clinical understanding of bleeding symptoms and management of Hemophilia A carriers, and the timing and intensity of carrier testing.

Results—Our survey indicates that 51% (36/51) of providers compared to 78% (36/46) of carriers believe that Hemophilia A carriers with normal FVIII activity have an increased bleeding tendency ($p<0.001$); 72% (33/36) of Hemophilia A carriers report a high frequency of bleeding symptoms. Regarding carrier testing, 72% (50/69) of medical providers recommend testing after 14 years of age, conversely 65% (29/45) of Hemophilia A carriers prefer testing to be done prior to this age ($p<0.001$).

Discussion—Hemophilia A carriers self-report a higher frequency of bleeding than previously acknowledged, and have a preference for earlier testing to confirm carrier status.

Keywords

Hemophilia A; carriers; bleeding; survey

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Introduction

While diagnosis and severity classification of Hemophilia A in males is based on factor VIII (FVIII) activity, identification of carriers is more challenging as the majority of Hemophilia A carriers have normal FVIII activity (>0.40 IU/mL) and there is inconsistent correlation of FVIII activity to bleeding symptom severity. The perception that bleeding symptoms in Hemophilia A carriers are clinically insignificant has led to a lack of investigation into the Hemophilia carrier bleeding phenotype (1).

Despite normal factor VIII activity (>0.40 IU/mL) Hemophilia A carriers have previously reported an increased bleeding tendency (2–6). These symptoms include, but are not limited to, epistaxis, easy bruising, menorrhagia, and post-operative surgical and dental bleeding (2). While together these data suggest that Hemophilia carriers demonstrate excessive bleeding, there has not been a direct comparison of provider and patient views.

Most Hemophilia advocacy organizations agree that genetic counseling should be done well in advance of pregnancy, however there is no unified recommendation of the optimal timing of Hemophilia carrier testing (7–9). Because of the lack of early carrier testing, Hemophilia carriers are not followed routinely at Hemophilia Treatment Centers. If Hemophilia A carriers truly have an increased bleeding phenotype it is reasonable to consider carrier testing prior to menstruation, the most commonly reported bleeding symptom in women with and without a bleeding disorder.

In order to obtain preliminary data and subsequently pursue a prospective study, we sought to elucidate the perceived discrepancy in belief of bleeding severity in Hemophilia A carriers. We developed an electronic survey to determine whether medical providers and Hemophilia A carriers have similar views about the severity of bleeding symptoms in Hemophilia A carriers. Our objective was to determine the attitudes and understanding of the Hemophilia A carrier bleeding phenotype, and opinions regarding carrier testing from the perspective of both medical providers and affected Hemophilia A carriers.

Material and Methods

Institutional Review Board approval was obtained at Vanderbilt University Medical Center. We employed a cross-sectional study design allowing us to collect data regarding opinions at a single time point. A cross-sectional design was appropriate for this study as there was no intervention and the majority of participants were expected to have ample historical experience with Hemophilia. An electronic survey was developed to understand bleeding symptoms in Hemophilia A carriers; questions were derived from the validated Female Universal Data Collection form (www.cdc.gov). The survey was emailed to physicians and nurses employed at U.S. Hemophilia Treatment Centers (HTC). The email list was generated from listed current HTC providers on www.cdc.gov. A similar electronic survey was developed and distributed to Hemophilia A carriers who were members of Hemophilia Federation of America. The inclusion criteria for medical providers was limited to those currently employed at a Hemophilia Treatment Center, and contact information on the

Center for Disease Control (CDC) website. The inclusion criteria for carriers was limited to self-report as a Hemophilia A carrier. There were no exclusion criteria.

The survey consisted of questions derived from the Female Universal Data Collection Registration form (10), and focused on the clinical understanding and management of Hemophilia A carriers. The summary of the survey is as follows: five questions focused on demographic information such as age and relationship to an affected male with Hemophilia; ten questions focused on the clinical care of Hemophilia A carriers, specifically the optimal timing of testing and previous clinical management; and seven questions on clinical bleeding symptoms (see figure 1 and 2). Data was collected by electronic return via automatic email of the survey directed into an online REDCap database (11), or by physical return of a paper survey, then entered into the database.

Sample size was calculated using PS: Power and Sample Size Calculation software developed by the Department of Biostatistics at Vanderbilt University. Prior data and expert opinion indicate that approximately 60% of Hemophilia A carriers self report increased bleeding symptoms, while 30% of medial providers believe Hemophilia A carriers have increased bleeding symptoms. Given these data, we needed at least 42 persons in each group to provide adequate comparisons with a power of 80% and a type 1 error probability of 0.05

Descriptive statistics were utilized for all survey questions. Responses of physician and nurses (medical providers) were compared using Pearson's Chi Squared test and Fisher's exact test when indicated. Responses of medical providers were compared using Pearson's Chi Squared test when data was normally distributed and Wilcoxon rank sum test when data was non-normally distributed. Only answers from obligate Hemophilia A carriers were analyzed. Obligate Hemophilia carrier was defined as a daughter of a male with Hemophilia A, mother of more than one male child with Hemophilia A, mother of a child with Hemophilia and another male family member with Hemophilia or a daughter to an obligate Hemophilia A carrier and another male member with Hemophilia A.

Results

There were 72 responses received from health care professionals at HTCs who provide care for children and adults with Hemophilia. All of the continental Hemophilia Treatment Center regions were represented in this sampling except for Region II (New York/New Jersey) and no more than 3 responses from each center were returned. The response rate was 49% (42/85) from the physicians and 37% (30/80) from the nurses. Characteristics of provider responses are shown in Table 1. Since there was no statistical difference between responses from nurses and physicians, and responses came from multiple Hemophilia Treatment Center regions, data was combined in subsequent analysis. There were 48 responses to the Hemophilia A carrier survey. The response rate and paired analysis could not be performed as the survey was distributed by Hemophilia Federation of American to protect the identity of members. Characteristics of obligate Hemophilia A carrier responses are shown in Table 2. There was occasional missing data, as a few respondents did not answer all of the questions, and thus denominators are provided for all questions. Only

responses from obligate Hemophilia A carriers, based on their self-reported family history, were analyzed for purposes of this study.

There is a discrepancy between the opinions of carriers and providers regarding the bleeding tendency of Hemophilia A carriers. When queried, 51% (36/71) of medical providers compared to 78% (36/46) of obligate carriers believe that Hemophilia A carriers with normal FVIII activity have an increased bleeding tendency ($p<0.001$). In sub-analysis of the medical providers, there was no difference in responses when stratified by clinical years of experience. In sub-analysis of the Hemophilia A carriers, there was no difference in responses when stratified by factor VIII activity (less than versus greater than 40% activity). Obligate Hemophilia A carriers surveyed had a self-reported mean FVIII activity of 48% (range 17–129) and 72% (33/36) report a high frequency of bleeding symptoms. Bleeding symptoms included menorrhagia (defined as >7 days of menstrual bleeding), post-pregnancy bleeding, oral bleeding, post-surgical bleeding, epistaxis and joint bleeding; providers also reported similar symptoms (Table 3). In sub-analysis, there was no statistical difference in the reported bleeding symptoms when stratified by factor VIII activity. The authors have specifically identified Hemophilia A carriers who report of significant menorrhagia, in some cases resulting in hysterectomy, and chronic joint problems, which carriers stated were secondary to joint bleeding earlier in life.

A discrepancy exists between the opinions of carriers and providers regarding the optimal timing of carrier testing. When asked about the optimal timing of carrier testing, 72% (50/69) of providers recommend testing after 14 years of age, conversely 65% (29/45) of obligate carriers prefer testing to be done prior to this age ($p<0.001$). The medical provider's report of their practice pattern is supported by the data collected in our survey, specifically the fact that 81% of carriers (34/42) state that they were not aware of their carrier status until after 14 years of age. In addition, 31% (15/46) of Hemophilia A carriers were never offered testing to confirm their carrier status. There was no difference in responses when stratified by clinical years of experience by the medical providers. Furthermore, 76% (35/46) of Hemophilia A carriers feel that they should be followed at a HTC due to their carrier status.

Discussion

Our results indicate that obligate Hemophilia A carriers surveyed through Hemophilia Federation of American, a patient advocacy organization, report excessive bleeding symptoms in contrast to the beliefs of medical providers who care for patients with a diagnosis of Hemophilia. The bleeding symptoms noted in our survey data are similar to previously published findings of Hemophilia A carriers with similar demographic information and factor activity (2, 3). Our survey as well as the previously reported data are not only consistent, but also emphasize the differences in bleeding tendencies reported when compared to a healthy population. In general, a healthy population of female adolescents and adults demonstrate menorrhagia in 35% (12), compared to the population of Hemophilia A carriers report that menorrhagia as defined by menstrual bleeding >7 days is present in over 50% in previously reported literature (2,3) and 94% in our current survey. This finding, along with other bleeding symptoms reported in our study and the two other concordant studies (2, 3), underscores the need for further investigation and education regarding

Hemophilia A carriers. Specifically, our study emphasizes the need for investigation into carrier testing in the pediatric population, as well as improved understanding of symptoms and their management in both the adult and pediatric populations.

In addition, our results demonstrate a difference in attitudes between patients and care providers regarding the timing of carrier status confirmation. Health care providers recommend that definitive carrier testing occur in adolescence or later as recommended by The American Academy of Pediatrics regarding genetic testing in children, while adult Hemophilia A carriers would prefer testing prior to adolescence as recommended by Canadian Hemophilia organizations (13). The belief of health care providers that testing for carrier status should be deferred until after adolescence could be linked to their belief that women do not experience significant bleeding symptoms at a younger age, thus no early medical intervention is anticipated. In addition, there is always the concern of insurance coverage of carrier testing, especially in a population that was historically considered to be asymptomatic. Testing prior to adolescence makes intuitive sense as nearly all of the adult Hemophilia A carriers self report menorrhagia, as this represents the first major hemostatic challenge in a woman's life. Based on this data we are currently investigating the timing of carrier testing in an ongoing prospective study.

Our study has a number of limitations. First, inherent to retrospective survey data is the presence of recall and selection bias. In addition to these generalizable phenomena, our voluntary survey could have resulted in over-reporting, especially given the involvement of members of a patient advocacy group. In addition, women were asked to provide their opinions about bleeding in Hemophilia A carriers in general despite the understanding that their experience may be limited to only themselves and/or friends. Second, our study included two separate surveys, while similar and necessary to collect data from two very different groups, this design provides inherent difficulty with comparisons. Third, we were unable to determine the total number of Hemophilia A carriers who were contacted to participate due to desires for anonymity within the Hemophilia Federation of America. The normal median and mean baseline factor VIII activity reported by carriers and involvement in a Hemophilia patient advocacy organization would argue that the respondents were likely typical Hemophilia A carriers and not patients with von Willebrand disease. Finally, the survey response rate of health care providers was moderately low at 44%, which introduces concern of selection bias. Despite these limitations, the survey response rate was the same or higher than previously published manuscripts (14, 15).

Our study indicates that both carriers and health care providers believe bleeding tendency occurs throughout a Hemophilia carrier's lifespan; however, carriers have a stronger belief that bleeding occurs more frequently when compared to health care providers. Based on this pilot data, we are currently conducting prospective studies confirming the bleeding phenotype of carriers and interrogating the optimal timing of carrier testing to corroborate these findings and prevent unnecessary bleeding.

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Hemophilia Carrier Survey

What best describes your occupation?	☐ Pediatric hematologist ☐ Adult hematologist ☐ Clinical nurse ☐ Research nurse ☐ Social Worker ☐ Physical therapist ☐ Other
If other occupation then please list your occupation.	_____
How many years have you been caring for patients with hemophilia?	☐ 0-5 years ☐ 6-10 years ☐ 11-20 years ☐ >20 years
What is your gender?	☐ Male ☐ Female
What best describes the location where you care for patients with hemophilia?	☐ University Hospital, non-HTC ☐ HTC within a University Hospital ☐ HTC separate from a University Hospital ☐ Private practice, non-HTC
Are you a hemophilia A carrier?	☐ Yes ☐ No
Do you provide hemophilia carrier A testing at your practice? (testing defined as FVIII activity or genetic testing)	☐ Yes ☐ No
MASAC (Medical Scientific Advisory Council) from the National Hemophilia Foundation recommends that potential hemophilia carriers should determine their status before they become pregnant. At what age do you feel hemophilia A carrier testing should be offered/performed?	☐ 0 - 12 months of age ☐ 1 - 5 years of age ☐ 6 - 10 years of age ☐ 11 - 14 years of age ☐ 15 - 18 years of age ☐ >18 years of age ☐ During pregnancy ☐ Only prior to minor or major surgeries ☐ I would not perform this testing
How should hemophilia A carrier status testing be done?	☐ FVIII activity only ☐ FVIII activity first and if < 50% no further testing ☐ FVIII activity and DNA testing ☐ DNA testing only ☐ Should not be performed
When should potential hemophilia A carriers see a genetic counselor regarding carrier status testing?	☐ Prior to testing ☐ Once test results have returned ☐ Before and after testing is done ☐ Never
Where should hemophilia A carrier testing be performed?	☐ Primary physician office ☐ Hemophilia Treatment Center
Do you believe that hemophilia carriers with normal FVIII activity (>40%) have an increased bleeding tendency?	☐ Yes ☐ No

If so what type of bleeding would you expect in a hemophilia carrier? (can choose more than one answer)

- ☐ Soft tissue bleeding
- ☐ Menorrhagia
- ☐ Joint bleeding
- ☐ Bleeding following pregnancy
- ☐ Oral bleeding
- ☐ Bleeding following surgery
- ☐ Epistaxis
- ☐ Recurrent miscarriages

What type of bleeding have you seen in hemophilia A carriers with normal (>40% FVIII) activity ? (Can choose more than one answer)

- ☐ Soft tissue bleeding
- ☐ Menorrhagia
- ☐ Joint bleeding
- ☐ Bleeding following pregnancy
- ☐ Oral bleeding
- ☐ Bleeding following surgery
- ☐ Epistaxis
- ☐ Recurrent miscarriages
- ☐ Prolonged skin bleeding
- ☐ None of the above

Figure 1.
Complete survey for medical providers.

Hemophilia Carrier Survey

The following is a survey that seeks to learn more about the attitudes about hemophilia carrier testing.

To qualify for the survey you must be a female obligate hemophilia A carrier defined as the following:Daughter of a male with Hemophilia A, mother of more than one male child with Hemophilia A, mother of a child with Hemophilia and another male family member with Hemophilia or a daughter to an obligate Hemophilia A carrier and another male member with Hemophilia A.

Are you a hemophilia A carrier? (note: We assume you are likely a carrier if your brother, son or father has hemophilia A (Factor 8 deficiency))	☐ Yes ☐ No ☐ I don't know
What severity of hemophilia A does your son, father or brother have? (note: Severe patients almost always require factor at least 1-2 times a week, moderate and mild patients usually only get factor when they bleed)	☐ Severe (less than 1% factor 8) ☐ Moderate (1-5% factor 8) ☐ Mild (6-40% factor 8) ☐ I don't know
What is your gender?	☐ Male ☐ Female
What is your age in years?	_____ (__ __ (no fractions))
What best describes your relationship to the patient with Hemophilia A?	☐ Mother, biologic ☐ Mother, adopted ☐ Mother, stepmother ☐ Sister, biologic ☐ Sister, adopted ☐ Sister, stepsister ☐ Daughter to a father with hemophilia ☐ none of the above
What best describes the location where your family member receives care for Hemophilia? (note: HTC: Hemophilia Treatment Center)	☐ University Hospital, non-HTC ☐ HTC within a University Hospital ☐ HTC separate from a University Hospital ☐ Private practice, non-HTC ☐ I don't know
Do you receive any regular care (at least clinic visits every 2 years) to manage your bleeding symptoms as a hemophilia A carrier?	☐ Yes ☐ No
Do you receive care at the same location as your brother or son with Hemophilia A?	☐ Yes ☐ No
Were you offered hemophilia carrier testing?	☐ Yes ☐ No
If yes, what specific carrier testing was performed?	☐ factor VIII (8) level check ☐ DNA testing (genetic testing) ☐ Not tested ☐ I don't know

At what age did you find you out that you are a hemophilia A carrier?	☐ 0 - 12 months of age ☐ 1 - 5 years of age ☐ 6 - 10 years of age ☐ 11 - 14 years of age ☐ 15 - 18 years of age ☐ >18 years of age ☐ I do not know my carrier status
What is your baseline or the lowest FVIII (Factor 8) level that you recall?	_____ (average is 50% (range 0-200%))
MASAC (Medical Scientific Advisory Council) from the National Hemophilia Foundation recommends that potential hemophilia carriers should determine their status before they become pregnant. At what age do you feel hemophilia carrier testing should be offered/performed?	☐ 0 - 12 months of age ☐ 1 - 5 years of age ☐ 6 - 10 years of age ☐ 11 - 14 years of age ☐ 15 - 18 years of age ☐ >18 years of age ☐ During pregnancy ☐ Only prior to surgeries or dental work ☐ Never ☐ I do not know
How should carrier status testing be done? (note FVIII: Factor 8 with normal being greater than 40-50%)	☐ FVIII activity only ☐ FVIII activity first and if < 50% no further testing ☐ FVIII activity and DNA testing ☐ DNA testing only ☐ Should not be performed ☐ I don't know
Were you offered counseling prior to conceiving your child about the possibility of having a child with hemophilia A?	☐ Yes ☐ No
When should potential hemophilia carriers see a genetic counselor about carrier status testing?	☐ Prior to testing ☐ Once test results have returned ☐ Before and after testing is done ☐ Never
Where should hemophilia carrier testing be performed?	☐ Primary physician office ☐ Hemophilia Treatment Center
If a patient is a confirmed hemophilia A carrier should they be followed in the Hemophilia Treatment Center?	☐ Yes ☐ No
Do you believe that hemophilia carriers with normal FVIII activity (>40%) have an increased bleeding tendency? (note FVIII: factor 8)	☐ Yes ☐ No
If so what type of bleeding would you expect in a hemophilia carrier with normal (>40%) FVIII levels? (note FVIII: factor 8) (Can choose more than one answer)	☐ Bleeding into the muscle ☐ Bleeding under the skin ☐ Heavy periods ☐ Bleeding into your joints ☐ Excessive bleeding after pregnancy ☐ Bleeding from your mouth ☐ Bleeding after a surgery ☐ Nosebleeds
Have you ever had a miscarriage?	☐ Yes ☐ No
If so, did your miscarriage occur in the first trimester (first 10-12 weeks of pregnancy)?	☐ Yes ☐ No
How many first trimester miscarriages have you had?	_____
How many total miscarriages have you had?	_____

Have you ever had any problems with bleeding?	☐ Yes ☐ No
If yes then please choose the type of bleeding that you have experienced in your life? (Can choose more than one answer)	☐ Bleeding into the muscle ☐ Bleeding under the skin ☐ Heavy periods ☐ Bleeding into your joints ☐ Excessive bleeding after pregnancy ☐ Bleeding from your mouth ☐ Bleeding after a surgery ☐ Nosebleeds
If you have heavy periods how long on average do your periods last (while not on birth control)?	☐ 1-5 days ☐ 6 days ☐ 7 days ☐ 8 days ☐ 9 days ☐ >10 days
Have you been given a blood transfusion because of a bleeding event?	☐ Yes ☐ No
If so what type of bleeding required the blood transfusion? (May choose more than one answer)	☐ Bleeding into the muscle ☐ Bleeding under the skin ☐ Heavy periods ☐ Bleeding into your joints ☐ Excessive bleeding after pregnancy ☐ Bleeding from your mouth ☐ Bleeding after a surgery ☐ Nosebleeds
Have you ever been given factor 8 concentrate because of a bleeding event?	☐ Yes ☐ No
If so what type of bleeding required the factor infusion? (May choose more than one answer)	☐ Bleeding into the muscle ☐ Bleeding under the skin ☐ Heavy periods ☐ Bleeding into your joints ☐ Excessive bleeding after pregnancy ☐ Bleeding from your mouth ☐ Bleeding after a surgery ☐ Nosebleeds
Have you ever been given plasma or Cryoprecipitate because of a bleeding event?	☐ Yes ☐ No
If so what type of bleeding event required the plasma or Cryoprecipitate? (May choose more than one answer)	☐ Bleeding into the muscle ☐ Bleeding under the skin ☐ Heavy periods ☐ Bleeding into your joints ☐ Excessive bleeding after pregnancy ☐ Bleeding from your mouth ☐ Bleeding after a surgery ☐ Nosebleeds
Have you ever been given Stimate or DDAVP because of a bleeding event?	☐ Yes ☐ No
If so what type of bleeding event required the DDAVP or Stimate? (May choose more than one answer)	☐ Bleeding into the muscle ☐ Bleeding under the skin ☐ Heavy periods ☐ Bleeding into your joints ☐ Excessive bleeding after pregnancy ☐ Bleeding from your mouth ☐ Bleeding after a surgery ☐ Nosebleeds

Figure 2.
Complete survey for Hemophilia A carriers.

Table 1

Characteristics of HTC Medical Providers

	Survey Responses, n (%)
Response rates by provider type	
Physician	42/85 (49)
Nurse	30/80 (37)
Experience (years)	
0 – 5	12/72 (17)
6 – 10	12/72 (18)
11 – 20	20/72 (28)
>20	27/72 (38)
Gender	
Male	28/71 (39)
Female	43/71 (61)
Haemophilia care setting	
University Hospital (non-HTC)	3/72 (5)
HTC	78/72 (94)
Private Practice	1/72 (1)
Availability of carrier testing at practice	
Yes	69/71 (97)
No	2/71 (3)
Surveillance of FVIII during pregnancy	
Yes	38/68 (56)
No	30/68 (44)
Timing in seeing a genetic counselor	
Prior to testing	14/71 (20)
Once test results are known	21/71 (30)
Before and after test results are known	33/71 (46)
Never	3/71 (4)

Table 2

Characteristics of Haemophilia A Carriers

	Survey Responses, n (%)
Age, mean year (+/− SD)	34+/− 11
Baseline FVIII activity (range)	48 (17 – 129)
Relationship to affected haemophiliae	
Mother	37/48 (78)
Sister	4/48 (8)
Daughter	4/48 (8)
None of the above	3/48 (6)
Severity of affected relative	
Mild	8/47 (17)
Moderate	9/47 (19)
Severe	30/47 (64)
Where affected relative receives care	
University Hospital (non-HTC)	4/46 (9)
HTC	35/46 (76)
Private Practice	7/46 (15)
Surveillance of FVIII during pregnancy	
Yes	38/68 (56)
No	30/68 (44)
Receive regular care for bleeding (at least every 2 years)	
Yes	11/45 (24)
No	34/45 (76)

Table 3

Bleeding Symptoms Noted by Survey Participants

	Survey Responses, n (%)
Haemophilia A Carriers	
What type of bleeding experiences have you had in your life?	
Soft tissue bleeding	19/32 (59)
Menorrhagia	30/32 (94)
Joint bleeding	5/32 (16)
Post pregnancy bleeding	21/32 (66)
Oral bleeding	14/32 (22)
Post surgical bleeding	13/32 (41)
Epistaxis	12/32 (38)
Physicians/Nurses	
What type of bleeding have you seen in Haemophilia A carriers?	
Soft tissue bleeding	31/72 (43)
Menorrhagia	58/72 (81)
Joint bleeding	21/72 (29)
Post pregnancy bleeding	35/72 (49)
Oral bleeding	3/72 (46)
Post surgical bleeding	43/72 (60)
Epistaxis	34/72 (47)