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Original Article

Evaluation of the bleeding symptoms in first-degree female relatives of patients with hemophilia A

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ABSTRACT

Objective: Carriers of hemophilia may have an increased bleeding tendency even if they have normal factor VIII levels. The aim of this study was to investigate the bleeding tendency with using a Bleeding Assessment Tool (BAT) in first-degree relatives of hemophilia A patients and to compare with women without family history of hemophilia or other bleeding disorders.

Material and Methods: First-degree relatives of hemophilia A patients (study group) were investigated prospectively evaluated and compared them with women without a family history of hemophilia or other bleeding disorders (controls group), including factor VIII levels, coagulation parameters and bleeding scores.

Results: The study included 30 women in the study group and 30 women in the control group. The mean FVIII levels in the study group and control group were 75.95±34.88 IU/m L and 112.83±25.44 IU/mL, respectively. In the study group, one woman had a moderate factor VIII deficiency (factor VIII level was 5 IU/mL). In addition, 4 women were found to have Factor VIII level between 5-39 IU/mL (24, 31, 36, and 39 IU/mL) which was compatible with mild factor VIII deficiency. Menorrhagia was the most common type of bleeding in the study group (83.3%), followed by cutaneous (60%) and oral cavity bleedings (56.6%). Menorrhagia, oral cavity bleeding and epistaxis were significantly more frequent in the study group compared to the control group ($p<0.001$, $p<0.001$, and $p<0.001$, respectively). No correlation was found between factor VIII level and bleeding score.

Conclusion: Our study showed that first-degree female relatives of hemophiliacs experienced at least one bleeding episode during their lifetime, regardless of factor VIII levels. Therefore, careful collection of bleeding histories in female relatives of hemophiliacs may help determine the necessary treatment methods to reduce mucosal and gynecologic bleeding.

Keywords: Bleeding tendency, Epistaxis, Hemophilia, Menorrhagia

INTRODUCTION

Hemophilia A, a deficiency of coagulation factor VIII (FVIII), is an inherited bleeding disorder that affects one in 5.000 male births (1). Females with a defective X chromosome are referred to as hemophilia carriers. The cellular mosaicism in the expression of the parental normal X chromosome allows the synthesis of normal FVIII in half of the FVIII -producing cells , while the other half express the defective FVIII gene and are therefore unable to produce the FVIII. However, FVIII levels vary from one carrier to carrier due to Lyonization, in which the expression of one of the two X chromosomes is randomly suppressed (1-3).

Carriers of hemophilia A usually have a sufficient (>40%) FVIII levels to control bleeding, but they may have an increased bleeding tendency even with normal FVIII levels (3). Age at diagnosis is usually delayed in hemophilia carriers compared to boys with hemophilia (4). Delayed diagnosis of a carrier with a potential bleeding risk may limit access to medical care (5). Recent studies have shown that carriers of hemophilia experience bleeding symptoms such as menorrhagia, postpartum hemorrhage, excessive postsurgical bleeding, epistaxis, easy bruising, and oral cavity bleeding (3,6). In this study, we aimed to investigate the bleeding tendency, bleeding scores, coagulation parameters, and FVIII levels in the first-degree female relatives of our patients with hemophilia A and compare our findings with those obtained in the women without family history of hemophilia or other bleeding disorders.

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MATERIALS and METHODS

This prospective study was conducted at Ankara Child Health and Diseases Hematology and Oncology Hospital, certified as the European Hemophilia Comprehensive Care Center, between June 2019 and January 2021. This study was approved by the local ethics committee (2019-211/ 27.06.2019). It was conducted in accordance with the latest version of the Declaration of Helsinki and good clinical practices. Informed consent was obtained from all participants.

First degree relatives (mothers and sisters) of hemophilia A patients who were being followed up in our hospital were included in the study group. We excluded women in the control group if they have a family history of hemophilia or other bleeding diathesis and also if they had a disease that could cause coagulation disorder or were taking medication. Women who admitted to our hospital for another reason and volunteered to participate in the study were recruited as the control group. Those who have vonWillebrand Factor deficiency or dysfunction, or other bleeding disorders, taking antiplatelet or anticoagulant medications or oral contraceptives, who have pregnancy, liver disease, malignancy, primary amenorrhea were excluded from the study.

Bleeding risk assessment

Bleeding risk assessment of the participants was determined by using the ISTH-BAT (International Society on Thrombosis and Hemostasis-Bleeding Assessment Tool) questionnaire (7). A physician (E.E.G) administered the questionnaire to the participants. Oral, muscular, cutaneous, gastrointestinal, surgical or trauma, tooth extraction, postpartum, and central nervous system bleeding, epistaxis, menorrhagia and hemarthrosis were evaluated. Each parameter was based on clinical criteria or treatments and rated from 1 to 4 depending on intensity and severity of the bleeding.

A bleeding score ranging from 0 to 56 points was determined by completing this 14-domain questionnaire. Bleeding risk assessment scores, factor VIII levels, and coagulation parameters were compared between the study and control groups.

Laboratory evaluation

Venous blood samples for measurement of activated partial thromboplastin time (aPTT) and FVIII, FIX, and vWF levels were drawn into tubes containing a standardized amount of sodium citrate (BD Vacutainer, 9NC 0,109M). The samples were centrifuged and processed in the coagulation laboratory of our hospital. Plasma aPTT and coagulation factor levels were measured by the Siemens Atellica COAG 360 (Erlangen, Germany) using standard kits according to the manufacturer's instructions. Plasma factor VIII levels were measured by means of a PTT-based one-stage assay method. Von Willebrand factor (vWf) levels and activity were assessed by enzyme-linked immunosorbent assay to exclude von Willebrand's disease. Factor VIII, FIX and activated partial thromboblastin time (aPTT) results of all participants were recorded for statistical analysis. Genetic analysis for hemophilia-causing mutations was not performed on individuals in the study and control groups.

Statistical Analysis

Data analysis was performed using SPSS Statistics for Windows, version 15.0 (SPSS Inc., Chicago, Ill., USA). The conformity of the variables to the normal distribution was examined by visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov tests). Analysis of data was primarily descriptive for continuous variables using standard deviations, minimum-maximum, mean, and median values. The Mann-Whitney U test was used for independent groups, and Chi-squared test was used to compare categorical variables. When $p<0.050$, the results were considered as statistically significant

RESULTS

Sixty-six women who were fisrt- degree relatives of 45 patients with hemophilia A followed up at our center were eligible for the study. Twenty-two participants did not agree to participate in the study and 14 participants did not meet the inclusion criteria.

Therefore, the study group comprised of 30 women. Thirty heatlhy volunteer women were recruited as the control group. Two of the five subjects in the study group were mothers of two hemophiliac children, and the other three were mothers of one hemophiliac child with a hemophiliac family member. The mean age of the subjects of study and control groups were 28.97± 8.60, and 29.10±8.06 (p=0.031), respectively.

There was no significant difference in mean aPTT values between the study and control groups (p=0.100). Two participants in the study group were found to have prolonged aPTT values. Individuals with prolonged aPTT values were found to have factor VIII levels of 5 IU/mL and 24 IU/mL, respectively. They were classified as having mild hemophilia. The mean FVIII level was statistically significantly lower in the study group (75.95± 34.88 IU/mL) compared to those in the control group (112.83 ±25.44 IU/mL;p<0.001). One women in the study group had a moderate factor VIII deficiency (factor VIII level was 5 IU/mL). In addition, 4 women were found to have Factor VIII levels between 5-39 IU/mL (24, 31, 36, and 39 IU/mL) which was compatible with mild factor VIII deficiency.

Comparison of the bleeding symptoms between the study and control groups is shown in Table I. Menorrhagia was the most common type of bleeding in the study group (83.3%) followed by cutaneous (60%), and oral cavity bleeding (56.6%).

Menorrhagia, oral cavity bleeding and epistaxis were significantly more frequent in the study group compared to the control group (p<0.001, p<0.001, and p<0.001, respectively). Although, cutaneous bleeding was the most common symptom

Table I: Distribution of bleeding in the Study and Control Group.

	Study Group	Control Group	p†
Menorrhagia*	25 (83.3)	11 (36.6)	< 0.001
Skin-subcutaneous bleeding*	18 (60)	19 (63.3)	0.800
Oral cavity associated bleeding*	17 (56.6)	3 (10)	< 0.001
Epistaxis*	14 (46.6)	3 (10)	<0.001
Postpartum bleeding*	2 (6.6)	1 (3.3)	0.550
Gastrointestinal tract bleeding*	1 (3.3)	1(3.3)	1
Surgical operation-related bleeding*	1 (3.3)	-	-
Total skin and mucosal bleeding*	78	38	<0.001
Bleeding after minor injury*	6 (20)	5 (16.6)	0.740
Tooth extraction related bleeding*	5 (16.6)	4 (13.3)	0.720
Bleeding of CNS*	-	1 (3.3)	-
Hemarthrosis*	-	1 (3.3)	-
Intramuscular bleeding	89	50	<0.001

***:** *n(%),* **†:** *Chi-squared test*

Table II: Bleeding scores of the study groups and control groups.

	Study Group*	Control Group*	p†	Obligatory Carrier*	Possible Carrier*	p†
Epistaxis	1 (1-4) *	1 (1-5)	<0.001	1 (1-4)	1 (1-4)	0.960
Oral cavity associated bleeding	2 (1-3) *	1 (1-3)	<0.001	2 (1-3)	2 (1-3)	0.590
Surgical operation-related bleeding	0 ((-1)-4)	0 (0-0)	0.310	0 ((-1)-4)	0 ((-1)-0)	0.830
Muscle hematoma	1 (1-1)	1 (1-5)	0.320	1 (1-1)	1 (1-1)	1
Skin-subcutaneous hemorrhage	2 (1-3)	2 (1-3)	0.110	2 (2-3)	2 (1-3)	0.110
Gastrointestinal tract bleeding	1 (1-2)	1 (1-3)	0.980	1 (1-1)	1 (1-2)	0.910
Menarche	2 (1-4) *	1 (1-5)	0.020	2 (2-4)	2 (1-4)	0.750
Hemarthrosis	1 (1-1)	1 (1-5)	0.320	1 (1-1)	1 (1-1)	1
Bleeding after minor injury	1 (1-3)	1 (1-3)	0.710	1 (1-3)	1 (1-3)	0.380
Tooth extraction related bleeding	1 ((-1)-3)	1 ((-1)-3)	0.980	1 ((-1)-2)	1 ((-1-)-3)	0.590
Postpartum bleeding	0 ((-1)-3)	0 (0-2) *	<0.001	(-1) ((-1)-3)	0 ((-1-)-3)	0.590
CNS bleeding	1 (1-1)	1 (1-5)	0.320	1 (1-1)	1 (1-1)	1
Total	13 (9-21)	13 (8-19)	0.550	14 (12-21)	13 (9-18)	0.070

:** *median (min-max),* **†:** *Mann-Whitney U test,* ***CNS: *Central nervous system*

in the control group (63.3%), it was not significantly different from the study group (60%). In the study group, 17 women (56.6%) experienced menorrhagia requiring medical assessment, three of whom (10%) were taking antifibrinolytics or oral contraceptivess. In five (16.6%) of the women from the study group menorrhagia caused anemia requiring curettage or iron treatment. None of the women in the study group required blood transfusion, desmopressin, factor replacement therapy, or hysterectomy due to menorrhagia. In the control group, four women (13.3%) experienced menorrhagia requiring medical assessment, and six (20%) had menorrhagia causing anemia requiring curettage or iron treatment. One (3.3%) woman in the control group had a history of blood transfusion due to menorrhagia.

Bleeding risk assessment showed that all of the women in the study and the control groups experienced at least one bleeding episode. Epistaxis and oral cavity bleeding scores were significantly higher in the study group compared to those in the control group (p<0.001, respectively). In the study group, 11 women (36.6%) experienced at least one oral cavity bleeding episode in their lifetime, and six of them required medical assessment. In the control group, two women experienced at least one oral cavity bleeding episode in their lifetime, and one required medical assessment. None of the participants in either group required surgical intervention, antifibrinolytics, blood transfusion, or factor replacement therapy for oral cavity bleeding. In the study group, 10 women (33.3%) had epistaxis more than five times

Table III: Comparison of study and control groups between FVIII level and bleeding susceptibility

Types of bleeding	Study Group				Control Group	
	Factor VIII level (IU/mL)			Total number of bleeding (n=30)	Factor VIII level (IU/mL)	Total number of bleeding (n=30)
	≤5 IU/mL (n=1)	5-40 IU/mL (n=4)	>40 IU/mL (n=25)		>40 IU/mL	
Menorrhagia	1	2	22	25	11	11
Skin and subcutaneous hemorrhages	1	3	14	18	19	19
Oral cavity bleeding	-	1	16	17	3	3
Epistaxis	1	3	10	14	3	3
Minor injury-related bleeding	-	-	6	6	5	5
Tooth extraction related bleeding	-	-	5	5	4	4
Postpartum hemorrhages	-	-	2	2	1	1
Gastrointestinal system bleeding	-	-	1	1	1	1
Surgery-related bleeding	-	-	1	1	-	0
Intramuscular hemorrhages	-	-	-	0	1	1
Hemarthrosis	-	-	-	0	1	1
Central nervous system related hemorrhages	-	-	-	0	1	1
Total	3	9	77	89	50	50

or lasting more than 10 minutes during their lifetime. Among them one had epistaxis requiring medical assessment, and three required medical intervention such as nasal tampon, cauterization, or antifibrinolytic drug administration. None of the women in the study group received blood transfusion, factor replacement therapy, or desmopressin for epistaxis. In the control group, one woman reported epistaxis more than five times or lasting more than 10 minutes; one woman required medical intervention for bleeding, and another one required blood transfusion. Menorrhagia scores were significantly higher in the study group than in the control group ($p = 0.020$). Two women in the study group had postpartum bleeding requiring blood transfusion; whereas only one woman in the study group required iron replacement therapy due to postpartum bleeding ($p<0.001$). Comparison of the median bleeding scores between the study and control groups is shown in Table II. There was no difference between FVIII levels and bleeding risk in hemophilia carriers and controls (Table III).

DISCUSSION

A woman with an affected X chromosome is called a hemophilia carrier (8). First-degree female relatives of hemophiliacs may be obligate or probable carriers of hemophilia, depending on whether they received the hemophilia gene from their father or mother, respectively (9). The World Federation of Hemophilia recommends genetic testing to identify carriers to define biology of the disease, to diagnose difficult cases, to estimate the risk of developing inhibitors, and to provide prenatal diagnosis (8). However, the facilities required for genetic evaluation may not always be adequate. Under these conditions, particularly in first-degree female relatives of hemophiliacs significant bleeding abnormalities may occur but be overlooked. The aim of this study was to determine the bleeding phenotypes of first-degree female relatives of our patients diagnosed with hemophilia A, their relationship with factor VIII levels, and to compare them with individuals without bleeding disorders.

In the study group, one woman had a moderate factor VIII deficiency, four women were found to have FVIII levels between 5-39 IU/mL (24, 31, 36, and 39 IU/mL) which was compatible with mild factor VIII deficiency. These individuals could be defined as having mild and moderate hemophilia according to the new classification. To eliminate confusion in the definition of hemophilia A carrier state, five clinical situations were defined in which personal bleeding history and baseline plasma FVIII levels were assessed. According to factor levels, women/girls with mild, moderate or severe

hemophilia (FVIII/IX >0.05 and <0.40 IU/ml, 0.01–0.05 IU/ml and <0.01 IU/ml, respectively) and hemophilia carriers with and without bleeding phenotype (FVIII level ≥0.40 IU/ml) were grouped (9). These results indicate that women who are relatives of hemophilia patients are at risk for bleeding and should be carefully monitored (10). Several studies using standardized bleeding assessment tools have reported that hemophilia carriers have increased bleeding scores compared to the general female population (11, 12).

The most commonly reported symptoms include menorrhagia, oral cavity bleeding, bleeding after tooth extraction, cutaneous bleeding, epistaxis and postsurgical bleeding and postpartum bleeding (11,13). Menorrhagia was the most common type of bleeding in the study group (83.3%) followed by cutaneous (60%) and oral cavity bleedings (56.6%). Menorrhagia, oral cavity bleeding and epistaxis were significantly more common in the study group than in the control group. In the review conducted by D'Oiron et al. (14), similar to our study, they reported that there was no significant relationship between FVIII levels and bleeding scores in hemophilia carriers.

A recent study from Türkiye in which sisters of 46 patients with hemophilia A or B were evaluated,reported that prolonged bleeding after minor injuries and tooth extraction was significantly higher in the sisters than in controls. Sisters also had longer menstrual periods compared to controls (15). Besides, the rate of postpartum bleeding was reported to be in the range of 13-22% in various studies (13,16,17). However, the rate of postpartum bleeding in our study was low, because of the relatively young age of the participants.

A retrospective study to determine the rate of joint disease in 539 potential hemophilia carriers revealed that the age of first hemarthrosis in women with FVIII level<50 IU/mL was earlier than in their healthy counterparts. They also noted that by the age of 60 years, 37% of the carriers had a joint disease, and they had a 2.3-fold higher risk for joint-related diagnoses compared with the general population (18). In our study, none of the women in the study group had hemarthrosis; however, one woman in the control group had hemarthrosis after trauma and required surgical intervention.

Coagulation reflects the balance between procoagulant and anticoagulant factors. Recent studies have investigated whether the FVIII mutation influences the bleeding phenotype in carriers. A correlation was shown between the severity of bleeding tendency in carriers and the type of FVIII gene mutation (19). However, another study found no correlation in bleeding scores or factor levels between carriers with null and non-null mutations (13).

One of the major limitations of our study was the lack of genetic analysis. Although it could not be determined whether the individuals in the study group were definitely hemophilia carriers, our findings are valuable in that they experienced more bleeding compared to the control group and show that hemophiliacs, especially their first-degree relatives, need to be monitored more closely. Another limitation of our study is that psychosocial aspects were not evaluated. In a previous study, the presence of psychological symptoms in individuals with hemophilia carriers has been noted (20).

In conclusion, our study showed that first-degree female relatives of hemophiliacs experienced at least one bleeding episode during their lifetime, regardless of factor VIII levels. Therefore, careful collection of bleeding histories in female relatives of hemophiliacs may help determine the necessary treatment methods to reduce mucosal and gynecologic bleeding.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Pediatrics Hematology Oncology Training and Research Hospital (27.06.2019, reference number: 2019-211).

Contribution of the authors

Genç EE: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Takingresponsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. **Güzelküçük Z:** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. **Koşan Çulha V:** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results. **Işık M**: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. **Gürlek Gökçebay D:** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. **Özbek NY:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/ study, Reviewing the article before submission scientifically besides spelling and grammar.

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Conflict of interest

The authors declare that there is no conflict of interest.

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