Published in final edited form as:

Haemophilia. 2015 November ; 21(6): 806–811. doi:10.1111/hae.12689.

Utility of a Pediatric Bleeding Questionnaire as a Screening Tool for von Willebrand Disease in Apparently Healthy Children

Nupur Mittal, Rachelle Pedersen, Paula James, Susan Shott, and Leonard A. Valentino

Rush University Medical Center and Queens University

Abstract

von Willebrand disease (VWD), an inherited bleeding disorder caused by deficiency or dysfunction of von Willebrand factor (VWF) is diagnosed when a personal and often a family history of excessive mucocutaneous bleeding is present along with abnormal laboratory studies. An accurate assessment of hemorrhagic symptoms is key in suspecting VWD but presents a challenge especially in children due to overlap between normal and abnormal bleeding. Bleeding questionnaire (BQ) scores have been validated in adults and have recently been validated in children with VWD for assessing bleeding severity. However there is limited data supporting their use prospectively in healthy children with bleeding complaints. The objectives of this study were to obtain normative data from children and validate a pediatric BQ to determine the discriminative ability of its total score and its individual components for identifying children likely to have VWD.

Methods—The pediatric BQ was administered to 1281 multiethnic, healthy children between 30 days and 18 years of age presenting to a general pediatric office and to 35 children with VWD based on VWF antigen, activity and multimer pattern.

Results—When children with total BQ scores of 3 or more were predicted to have VWD, the sensitivity was 97.2%, the specificity was 97.1%, the positive predictive value was 48.6%, and the negative predictive value was 99.9%.

Conclusions—The pediatric BQ may help discriminate a significant bleeding history from otherwise trivial bleeding and may be integrated into the primary care algorithm for evaluating children suspected of having VWD.

Introduction

von Willebrand disease (VWD) is an inherited bleeding disorder caused by deficiency or dysfunction of von Willebrand factor (VWF), a plasma protein that mediates the adhesion of platelets at sites of vascular injury and also binds to and stabilizes blood coagulation factor VIII (FVIII) thereby prolonging its half-life in the circulation. Deficiency or defects in the function of VWF can cause bleeding by impairing platelet adhesion or reducing the concentration of FVIII in the plasma.

VWD is the most common bleeding disorder but its prevalence varies considerably among studies and depends largely on the case definition used. The prevalence has been estimated in several countries on the basis of the number of symptomatic patients seen at specialized haemostasis centers, and ranges from roughly 23 to 110 per million population [1]. VWD is

classified into three major categories: partial quantitative deficiency (type 1), qualitative deficiency (type 2), and total deficiency (type 3). Type 2 VWD is further subdivided further into four variants (2A, 2B, 2M, 2N) on the basis of the laboratory phenotype [2,3].

Three key features form the basis for diagnosis: a personal history of excessive mucocutaneous bleeding, the hallmark of the disease, a family history of the same, and abnormal VWF laboratory studies [4]. Most often, bleeding includes excessive and/or unexplained bruising, epistaxis, bleeding from the gums and from trivial wounds, and in females, menorrhagia and postpartum hemorrhage. Prolonged and excessive bleeding may also occur after surgical and dental procedures.

Children who have VWD also may experience bruising after routine immunizations and gum bleeding after the loss of primary teeth. Typically, only patients who have type 3 VWD experience spontaneous musculoskeletal bleeding, typical of patients who have severe hemophilia.

Children have had fewer exposures to bleeding challenges such as surgery, dental extractions, menses and childbirth. In addition, certain bleeding symptoms, such as cutaneous bruising and epistaxis may be reported by healthy children due to physiologic differences. For these reasons, an accurate assessment of haemorrhagic symptoms is key in diagnosing VWD but often presents a significant challenge in the pediatric population. This challenge may manifest in the pediatrician's office at first presentation. Evaluation of bleeding and interpretation of symptoms involves the collection of data using objective, standardized criteria and clinical judgment. Next, the data must be interpreted to determine if the bleeding history is compatible with a bleeding disorder and, if so, how severe the bleeding disorder could be. It is in this regard that bleeding questionnaires (BQ) have played a major role. In adults, questionnaires have been evaluated and validated for the diagnosis of VWD. The first reported application of a BQ was by Rodeghiero et al [5]. Since then, several questionnaires have been evaluated and validated for assessing severity of VWD in children and, more recently, diagnosing a bleeding disorders in children presenting to the office with bleeding complaints. Along with these questionnaires, the pediatric BQ studied here could be a reliable tool to validate clinical diagnostic criteria of VWD. This BQ produces a quantitative index that summarizes the number of bleeding episodes and their severity. The BQ total score has shown good sensitivity and specificity for the diagnosis of type 1 VWD in adults and could be integrated into a full diagnostic algorithm that also takes into consideration the laboratory and family data for children [6, 7].

The aims of the present study were to: 1) derive normative data with respect to the BQ total score in a population of healthy children; 2) evaluate the discriminative capability of the BQ for identifying children with pathological bleeding within an apparently healthy pediatric population; and 3) determine whether the BQ can identify children with a known diagnosis of VWD.

Methods

This research was reviewed and approved by the Institutional Review Board of Rush University Medical Center. Consecutive healthy children between 30 days and 18 years of age without a diagnosis of a chronic medical condition presenting to a general pediatrician's office for routine or sick visits were eligible for enrollment. Participants with a known bleeding disorder or with a chronic illness were excluded.

To obtain normative data in this population of healthy children, the pediatric BQ [8] was administered by one investigator (NM). Recruitment was done in an ambulatory pediatric clinic of Rush University Medical Center (n = 1001) and in a private pediatric practice office (n = 280). Bleeding scores were calculated as previously published [8]. The threshold for an abnormal score was ≥ 3 . Laboratory testing for VWD was not performed in this group of patients.

Thirty-five children (average age 9.1 years and 40% female) with a known diagnosis of VWD on the basis of VWF antigen levels, ristocetin cofactor activity and multimer analysis according to diagnostic criteria for VWD from Hospital for Sick Children were also enrolled.

The pediatric BQ [8] assesses the presence and severity of bleeding symptoms including epistaxis, easy bruising, bleeding from minor wounds, oral cavity bleeding, bleeding after dental or surgical procedures, gastrointestinal tract bleeding, menorrhagia, and an 'Other' category which includes post-venipuncture bleeding, macroscopic hematuria, and pediatric-specific symptoms (umbilical stump bleeding, cephalohematoma, and post-circumcision bleeding).. Scoring is based on a scale ranging from 0 to 4 in most categories and -1 to 4 in some categories, with four representing the most severe symptoms [Table 1]. The questions were answered by the parents in case of children less than 12 years and by the child if 12 years or older and developmentally capable to do so with parents being present throughout.

SPSS for Windows (Version 16) was used for data management and statistical analysis. The Mann-Whitney test was done to compare the healthy and VWD groups with respect to the BQ total score. Univariate logistic regression analyses with likelihood ratio *p*-values were done to evaluate the BQ total score and its components with respect to their ability to distinguish between healthy subjects and subjects with VWD. Sensitivity, specificity, and positive and negative predictive values were calculated. A 0.05 significance level was used for all statistical tests. No one-sided tests were done.

Results

The demographic characteristics of the two groups are shown in Table 2. Among healthy subjects, 43% were female and about half were African-American. In contrast, the ethnicity of the VWD subjects was primarily Caucasian and Hispanic. The median age of the two groups was similar (4.6 and 5.0 years).

The BQ scores (mean $\pm$ SEM) for each of the individual questions are shown in Figure 1. Among the healthy children, epistaxis and oral bleeding had the highest mean scores (Figure

1A), while epistaxis and wound bleeding had the highest scores in children with VWD (Figure 1B). It should be noted that although the patterns of the bar graphs are similar, the scales for their y-axes differ by a factor of 10. The BQ total score for the healthy children ranged from 2 to 5 with a mean of 0.31 ± 0.02 , compared to a range of 0 to 21 with a mean of 6.97 ± 0.81 for those with VWD ($p < 0.001$).

Logistic regression was done using the BQ total score to predict VWD. This score was highly statistically significant ($p < 0.001$), with a sensitivity of 97.2%, a specificity of 97.1%, a positive predictive value of 48.6%, and a negative predictive value of 99.9% when children with BQ total scores of 3 or more were predicted to have VWD. To assess the discriminative ability of each bleeding symptom in the diagnosis of VWD, a univariate logistic regression analysis was done for each symptom. The results are shown in Table 3. Cutaneous symptoms and epistaxis had the highest sensitivity but lower specificity compared to muscle, joint and surgical bleeding and menorrhagia.

Discussion

The importance of a sound history cannot be overemphasized in the diagnosis of VWD. Bleeding manifestations are frequent among healthy children, hence raising the question of whether history alone can be relied upon to provide accurate screening for VWD in children and in determining whom to refer for further investigations.

In addition, the validation of BQ in adults in the recent past for diagnosis of VWD raises the question of their utility in children given the often unique and early presentations such as post circumcision and umbilical stump bleeding and the non-specific nature of bleeding complaints in children.

Bleeding assessment tools (BAT) have been developed and studied in a variety of clinical settings [5,6,9-12]. These tools are invaluable in the identification of symptomatic patients given a prevalence of 1 in 1000; however, a review of diagnosed cases reveals that far fewer patients have been diagnosed, and therefore, have access to appropriate treatment. This is also likely to be true for children presenting to the pediatrician's office with bleeding complaints.

von Willebrand disease is the most common bleeding disorder as estimated in 2 large studies, one by Rhodigero et al in Italian school children [13] and the other a multiethnic American sample examined by Werner et al [14]. Neither study focused on the prevalence in individuals with symptomatic bleeding. This accounts for the discrepancies in the estimated prevalence of VWD and the referral rates to tertiary centers for evaluation for VWD. Using the history as conveyed by a BAT, which evaluates the most common bleeding symptoms, provides a useful guide when deciding who to test and may improve the positive predictive value of the laboratory tests for VWD.

The original BAT was the Vicenza Bleeding Questionnaire [13]. Over the years various modifications of this tool have been made, including the Condensed MDMCM-1 VWD Bleeding Questionnaire developed and prospectively validated by the group at Queen's University, Kingston, Ontario, Canada in a predominantly adult population [9]. This

questionnaire has a sensitivity of 100%, specificity of 87%, positive predictive value of 0.20, and negative predictive value of 1.0. A subsequent, pediatric-specific version called the Pediatric Bleeding Questionnaire (PBQ), that was used in this study was been developed and validated, although given the lack of hemostatic challenges in children, it is less sensitive compared with instruments used in adults. The sensitivity, specificity, positive predictive value and negative predictive value of the PBQ were 83%, 79%, 0.14, and 0.99 respectively in an earlier study [8]. The ISTH-BAT, which was published in 2010 [10], is the most recent version and builds on the knowledge of the previous Vicenza based BATs, with modifications which capture the frequency of bleeding episodes more accurately.

A study done recently in Ontario Canada by Bowman et al used the Condensed MDMCM-1 VWD Bleeding Questionnaire and focused on subjects presenting with concerning bleeding symptoms. They found the prevalence of VWD for these subjects at the level of primary practice to be 0.09%. These authors used a cutoff value of 4 for an abnormal bleeding score. However, this study enrolled primarily adults, with only one subject who was less than 15 years old [9]. Subsequently, they evaluated a pediatric population with the PBQ and found the prevalence of VWD in symptomatic children at the level of pediatric primary care practice to be 0.11% [15]. The main limitation of both of these studies was that many of the subjects could not be tested for VWD due to lack of consent. Marcus et al evaluated the Vicenza bleeding score prospectively in 104 subjects in a tertiary care pediatric setting and found that it had a low positive predictive value but a good negative predictive value to exclude VWD [16].

In another study, also from Ontario, Canada, Biss et al [17] evaluated the PBQ in a large cohort of children with VWD and a smaller cohort of their healthy siblings. The median bleeding score was 7 in this population with a similar profile of significant bleeding symptoms as in our population.

Our main objective was to evaluate the utility of an easily administered questionnaire to assess bleeding symptoms in the primary care setting. This is especially important in the case of children who report bleeding symptoms since use of this questionnaire could facilitate referral to a specialist for further testing.

A limitation of the present study is that testing of the healthy subjects with an elevated total score was not done, so we could not assess the predictive value of the PBQ in apparently healthy children.

In conclusion, the PBQ may help clinicians distinguish between a significant bleeding history and trivial bleeding common among children. If properly used, the PBQ could be integrated into an algorithm to evaluate children suspected of having a bleeding disorder such as VWD. BATs can distinguish between normal persons and persons with a bleeding disorder, identify those at risk of having a bleeding disorder and those who are very unlikely to have a bleeding disorder, and describe disease severity within a limited spectrum. This may be valuable in the pediatrician's office, since children often present with bleeding symptoms, which may not be significant, and BATs could aid in determining who to refer.

References

1. Sadler JE, Mannucci PM, Berntorp E, et al. Impact, diagnosis and treatment of von Willebrand disease. *ThrombHaemost.* Aug; 2000 84(2):160–174.
2. Mittal N, James P, Valentino LA. Diagnosis of Von Willebrand Disease in Children. *Current Pediatric Reviews.* 2009; 5(3):169–175.
3. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia.* 2008; 14(2):171–232. [PubMed: 18315614]
4. Sadler JE, Budde U, Eikenboom JC, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. *J ThrombHaemost.* 2006; 4(10):2103–14.
5. Rodeghiero F, Castaman G, Tosetto A, et al. The discriminant power of bleeding history for the diagnosis of von Willebrand disease type 1: an international, multicenter study. *J ThrombHaemost.* 2005; 3:2619–26.
6. Tosetto A, Rodeghiero F, Castaman G, et al. A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1VWD). *J Thromb Haemost.* 2006; 4(4):766–773. [PubMed: 16634745]
7. Tosetto A, Castaman G, Rodeghiero F. Bleeding scores in inherited bleeding disorders: clinical or research tools? *Haemophilia.* 2008; 14(3):415–6. [PubMed: 18218013]
8. Bowman M, Riddel J, Rand ML, et al. Evaluation of the diagnostic utility for von Willebrand disease of a pediatric bleeding questionnaire. *J Thromb Haemost.* 2009; 7:1418–21. [PubMed: 19496919]
9. Bowman M, Mundell G, Grabell J, et al. Generation and validation of the Condensed MCMDM 1VWD Bleeding Questionnaire for von Willebrand disease. *J Thromb Haemost.* 2008; 6:2062–6. [PubMed: 18983516]
10. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. *J Thromb Haemost.* 2010; 8:2063–5. [PubMed: 20626619]
11. Berntorp E, Peake I, Budde U, Laffan M, Montgomery R, Windyga J, Goodeve A, Petrini P, von Depka M, Miesbach W, Lillicrap D, Federici AB, Lassila R, White G. von Willebrand's disease: a report from a meeting in the Åland islands.
12. Tosetto A, Castaman G, Rodeghiero F. Assessing bleeding in von Willebrand disease with bleeding score. *Blood Rev.* 2007; 21(2):89–97. [PubMed: 16774804]
13. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood.* 1987; 69:454–9. [PubMed: 3492222]
14. Werner EJ, Broxson EH, Tucker EL, et al. Prevalence of von Willebrand disease in children: a multiethnic study. *J Pediatr.* 1993; 123:893–8. [PubMed: 8229521]
15. Bowman M, Hopman WM, Rapson D, Lillicrap D, Silva M, James P. A Prospective Evaluation of the Prevalence of Symptomatic von Willebrand Disease (VWD) in a Pediatric Primary Care Population. *Pediatric Blood & Cancer.* 2010; 55:171–173. PMID: 20213845. [PubMed: 20213845]
16. Marcus PD, Nire KG, Grooms L, Klima J, O'Brien SH. The power of a standardized bleeding score in diagnosing paediatric type 1 von Willebrand's disease and platelet function defects. *Haemophilia.* 2011; 17(2):223–227. [PubMed: 20860605]
17. Biss TT, Blanchette VS, Clark DS. Quantitation of bleeding symptoms in children with von Willebrand disease: Use of a standardized pediatric bleeding questionnaire. *J Thromb Haemost.* 2010; 8:950–956. [PubMed: 20136710]

Figure 1.

Individual component bleeding scores for healthy (A) and VWD subjects (B). The mean and standard error are shown. Note that there is a 10-fold difference in the range for the y-axis between the two graphs.

Table 1

Scoring key for the Pediatric Bleeding Questionnaire. In the last row, the symptoms included in the "Other" category are umbilical stump bleeding, cephalhematoma, post-circumcision bleeding, post-venipuncture bleeding, and macroscopic hematuria

Score	-1	0	1	2	3	4
Symptom						
Epistaxis	-	No or trivial (5 per year)	>5 per year OR >10 minutes duration	Consultation only	Packing, cauterization or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Cutaneous	-	No or trivial (1cm)	>1cm AND no trauma	Consultation only	-	-
Minor wounds	-	No or trivial (5 per year)	>5 per year OR >5 minutes duration	Consultation only or Steri-strips	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Oral cavity	-	No	Reported at least once	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Gastrointestinal tract	-	No	Identified cause	Consultation or spontaneous	Surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy or desmopressin	-
Tooth extraction	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing, repacking or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Surgery	No bleeding in at least 2 surgeries	None done or no bleeding in 1	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Menorrhagia	-	No	Reported or consultation only	Antifibrinolytics or contraceptive pill use	D&C or iron therapy	Blood transfusion, replacement therapy, desmopressin or hysterectomy
Post-partum	No bleeding in at least 2 deliveries	No deliveries or no bleeding in 1 delivery	Reported or consultation only	D&C, iron therapy or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin	-
Muscle hematoma	-	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	-	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system	-	Never	-	-	Subdural, any intervention	Intracerebral, any intervention

Score	-1	0	1	2	3	4
Symptom						
Other *	-	No	Reported	Consultation only	Surgical hemostasis, antifibrinolytics or iron therapy	Blood transfusion, replacement therapy or desmopressin

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Subject Demographic Characteristics and Total BS

	Healthy Subjects (n = 1281)	VWD Subjects (n = 35)
Females, n (%)	554 (43.2)	14 (40.0)
Mean age $\pm$ SD (yr)	5.5 $\pm$ 4.6	9.1 $\pm$ 5.0
Ethnicity, no (%)		
African American	603 (47.1)	2 (5.7)
Asian	34 (2.7)	1 (2.9)
Caucasian	369 (28.8)	21 (60)
Hispanic	271 (21.2)	11 (31.4)
Other	2 (0.2)	0
Median Total BS (range)	0 (−2, 5)	6 (0, 21)

Table 3

Results of Univariate Logistic Regression to Predict VWD

Variable	Sensitivity	Specificity	Positive	Negative	P-Value
			Predictive Value	Predictive Value	
Epistaxis	60.0	93.4	20.0	98.8	< 0.001
Cutaneous symptoms	82.9	94.7	29.9	99.5	< 0.001
Bleeding from minor wounds	57.1	99.0	60.6	98.8	< 0.001
Oral cavity bleeding	51.4	93.3	17.3	98.6	< 0.001
GI bleeding	34.3	96.2	19.7	98.2	< 0.001
Bleeding after tooth extraction	8.6	99.3	25.0	97.5	0.004
Bleeding after surgery	22.9	99.8	72.7	97.9	< 0.001
Menorrhagia	22.9	99.7	66.7	97.9	< 0.001
Muscle hematomas	17.1	100	100	97.8	< 0.001
Hemarthrosis	14.3	100	100	97.7	< 0.001
CNS bleeding	5.7	100	100	97.5	< 0.001
Other	14.3	97.2	12.2	97.6	0.005