Clinical Features and Types of Von Willebrand Disease in Women with Menorrhagia Referred to Hematology Clinic of Kermanshah

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ABSTRACT
Menorrhagia is the most common symptom that is experienced by women with bleeding disorders. Von Willebrand disease (VWD) is the most common congenital human bleeding disorder that is manifested as a quantitative deficiency in Von Willebrand factor (VWF) or dysfunction of this factor. The frequency of VWD is similar in both men and women. However, VWD is more readily detected in women due to the presence of severe bleeding associated with menstrual cycles and childbirth. The present study was carried out to find the frequency of VWD, its types, and clinical features of the disease among women with menorrhagia who referred to the Hematology Clinic of the Kermanshah University of Medical Sciences. The study comprised 482 women with menorrhagia. After excluding patients with confounding factors, 56 (11.6%) patients were evaluated for inherited bleeding disorders. We detected 31 (55.3%) patients with VWD. Type 3 of VWD was the most frequent subtype (45.2%) followed in frequency by type 2 (32.3%), and type 1 (22.5%). In conclusion, our study indicated that menorrhagia can be the first symptom of VWD. Therefore, rare coagulation disorders should be considered in women with idiopathic menorrhagia, particularly in regions with high rates of consanguinity.

KEY WORDS: Menorrhagia, Von Willebrand disease, Bleeding disorders, Coagulation disorders

INTRODUCTION
Menorrhagia is a common complaint in women of reproductive ages. This condition is manifested in around 5% of women aged between 30 and 491 and comprises 12% of all gynaecology referrals.2 The etiology of the condition may be local or systemic but a specific cause is identified in less than 50% of affected women.3 Recently it has been suggested that bleeding disorders, specially von Willebrand disease (VWD) and platelet function (PFD) disorders, are more prevalent in women with menorrhagia.4, 5 A prevalence of 1% has been found for VWD in the general population. However, in women with menorrhagia, a higher prevalence of 10% to 20% has been reported.4 Von Willebrand disease is classified into partial quantitative deficiency (type 1) that consists 70 % to 80% of all VWD cases, qualitative deficiency (type 2) that
occurs in 20% of VWD cases, and total deficiency (type 3) which occurs in around 5% to 10% VWD cases resulting in secondary severe deficiency of FVIII. According to the phenotype type 2 VWD is divided into 4 variants (2A, 2B, 2M, 2N). Type 1 von Willebrand disease is usually mild and affected women may not have problems until faced with a haemostatic challenge, such as menstruation or childbirth. So, screening of women with menorrhagia is an excellent way for detection women with this disorder. Establishing a diagnosis of von Willebrand disease, especially in its mild form, is difficult and complex. In the absence of genetic diagnosis, a combination of clinical features and laboratory assessment of von Willebrand factor antigen (VWF:Ag), von Willebrand factor functional activity (VWF:FAc) or FVIII assay will be useful in the diagnosis of cases. The level of these coagulation factors in plasma is influenced by many factors such as age, race and blood group. Also, there is variation in the levels of these factors in the same woman at different phases of the menstrual cycle. The prevalence of VWD has not been determined in Western Iran. The present study was carried out to investigate the frequency of VWD, its subtypes, and the clinical features of the disease among women with menorrhagia who referred to the Hematology Clinic of the Kermanshah University of Medical Science, in Kermanshah, Western Iran, with Kurdish ethnic background.

**MATERIALS AND METHODS**

The present study was performed at the Central Hematology Clinic of Kermanshah city from August 2010 to May 2012. We investigated 482 women with menorrhagia. According to declaration of Helsinki; informed written consent was obtained from all adult participants, parents, or legal guardians. Patients were screened for a history of congenital bleeding disorders or suspected bleeding tendencies. Patients known to have acquired VWD, immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), or on anticoagulant therapy were excluded from the study. A washout period of 7 days was set before blood samples were taken for analysis. The demographic and clinical features of each patient including age, age at menarche, family history, history of drug consumption, menstrual history, quantity of bleeding and associated dysmenorrhoea or other symptoms were obtained in a questionnaire. The laboratory investigations included the evaluation of haemoglobin, packed cell volume, blood grouping, platelet count, bleeding time (BT), clot retraction, clotting time (CT), peripheral smear, prothrombin time (PT), activated partial thromboplastin time (APTT) and inhibitor screening and correction studies. For coagulation assays, venous blood samples were collected in tubes containing 0.109 M (3.2%) trisodium citrate in a ratio of 9 parts blood to 1 part anticoagulant and then centrifuged without delay at 1200 G for 15 minutes. The remaining plasma was stored in 2 aliquots at 7°C for factor assay, VWD diagnosis, and detection of subtypes. Blood sample for CBC collected in EDTA tubes and was detected using Sysmex XE-2100 (Kobe, Japan). Detection of PT, APTT, factor VIII levels, and VWF: Ag was performed using Sysmex CA-1500 (Kobe, Japan) by appropriate quality control materials and standard reagents (Dade Behring, Germany). PT, aPTT, and BT were detected using standard techniques, and factor assays were done by one-stage coagulometric method (factor VIII normal range: 50-150%). Clauss method was used for fibrinogen assay and BT was identified by Ivy’s modified template method. Von Willebrand’s factor: Ag was analyzed using Diagnostica Stago reagent, calibrated on Sysmex CA-1500. Test was based on immuno-turbidimetric method (normal range: 50-160 %) while Ristocetin cofactor assay (RiCoF) was carried out using stabilized platelets agglutinated in the presence of VWF and the antibiotic ristocetin on AggRAM (manufactured for Helena BioSciences Europe). Ristocetin-induced platelet aggregation (RIPA) was done on AggRam (Helena Laboratories) using platelet rich plasma (PRP) with a count adjusted to 200 to 250 × 10^5/L. Local reference ranges were calculated for these tests in our laboratory on healthy male and female individuals, n = 80. Von Willebrand disease was classified on the basis of criteria developed by the VWF Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH), first published in 1994 and revised in 2006. The RiCoF to VWF: Ag ratio of...
<0.7 was used for differentiating type 1 from type 2 VWD. Type 3 VWD was characterized by undetectable to less than 10 % VWF protein with markedly decreased activity and very low FVIII levels (1-9 IU/dL). All statistical analysis was performed by using SPSS software version 16.0. Frequency and percentage were computed for categorical variables and mean and standard deviation were estimated for quantitative variables.

RESULTS

After excluding patients with confounding factors, 56 (11.6%) patients were evaluated for inherited bleeding disorders in our center and 31 (55.3%) patients had VWD. The mean age of studied individuals was 24.4 ± 8.9 years. Participants included 18 adolescent women 19 years or younger, 18 women between 20 and 44 years, and 5 perimenopausal-age women 45 years or older. Type 3 was the most frequent with a prevalence of 45.2% (14 out of 31), type 2 was the second prevalent type, 10 out of 31 (32.3%), and finally there were 7 out of 31 women (22.5%) with type 1. The assessment of blood loss during menstruation was done by checking detailed history of pad/tampon changing. In 15/31 (48.38%) cases, heavy blood loss, amounting to approximately more than 100 ml/cycle was seen, whereas in the remaining 16/31 cases (51.61%), there was moderate loss of blood. In type 3, presentation was similar to patients with hemophilia having hemarthrosis (37.5 %) and hematomas (43.7%). Other types of bleeding which were noted in our study included epistaxis, posttraumatic gum bleeding and etc. which are shown in Table 1.

| Table 1. Clinical Spectrum of Von Willebrand Disease |
|---------------------------------------------|
| Clinical Spectrum | Count | Percentage |
|------------------|-------|-------------|
| Hematoma         | 10    | 32.2        |
| Gum bleeding     | 8     | 25.8        |
| Epistaxis        | 3     | 9.6         |
| Bleeding after trauma | 6 | 19.3       |
| Bruises          | 3     | 9.6         |
| Hemarthrosis     | 7     | 22.5        |

Further, 22 (70.9%) women reported a history of anemia, and 19 (86.3%) of these women reported receiving treatment for anemia. Pack red cells transfusion was given to two patients of hemoglobin less than 6.0 g/dl with signs of anemia. Fifteen women had hypochromic microcytic anemia, with hemoglobin less than 12 g/dl and were treated with iron supplements, oral contraceptives (combination of estrogen–progesterone), antifibrinolytic agents (tranexamic acid), alone or in combination. There were 3 out of 31 cases with a positive family history and all of them were found to have haemostatic disorder. Of 24 women with type 2 and type 3, 21 women received Humate-P therapy. The various laboratory parameters in our patients are shown in Table 2.

| Table 2. Laboratory Parameters and Blood Groups with Respect to Type of VWD |
|---------------------------------|-----------------|-----------------|-----------------|
| Characteristic                  | Type 1 n= 7 Mean ± SD | Type 2 n= 10 Mean ± SD | Type 3 n= 14 Mean ± SD |
| Hemoglobin (g/dL)               | 12.14 ± 3.41     | 11.02 ± 2.82     | 9.32 ± 2.64     |
| MCV (fl)                        | 68.94 ± 22.64    | 65.76 ± 18.13    | 67.46 ± 12.71   |
| MCH (pg)                        | 22.37 ± 6.45     | 2152 ± 11.85     | 20.41 ± 7.24    |
| Platelet (× 10^9/L)             | 290.64 ± 68.6    | 308.24 ± 98.24   | 316.61 ± 48.32  |
| PT (min)                        | 2.54 ± 1.32      | 3.67 ± 1.21      | 8.97 ± 1.14     |
| APTT (sec)                      | 10.33 ± 0.54     | 10.28 ± 0.63     | 10.51 ± 0.32    |
| Factor VIII (%)                 | 43.32 ± 25.42    | 6981 ± 49.65     | 5.01 ± 4.32     |
| VWF:Ag (%)                      | 41.29 ± 6.65     | 7983 ± 39.85     | 2.01 ± 1.98     |
| RiCoF (%)                       | 93.25 ± 15.75    | 2486 ± 12.35     | 4.12 ± 3.85     |
| RIPA (%)                        | 82.31 ± 39.85    | 7945 ± 11.9      | 15.19 ± 22.31   |
| RiCoF/VWF:Ag ratio              | 2.65 ± 1.65      | 0.25 ± 0.19      | 0.27 ± 0.18     |
| Blood group                     |                 |                 |                 |
| A                               | 2                | 2                | 3               |
| B                               | 1                | 1                | 2               |
| AB                              | 1                | 1                | 1               |
| O                               | 3                | 4                | 6               |
| Not available                   | 0                | 2                | 2               |
DISCUSSION

Menorrhagia, or heavy menstrual bleeding (HMB), is the most common symptom that women with bleeding disorders experience. The average menstrual blood loss is 25–80 ml without significant clots. This definition is taken from population studies, which have shown that approximately 10% of women experience losses of over 80 ml per cycle. Normal coagulation processes are needed to stop blood loss due to shedding of the endometrial lining and blood vessels. In some cases, bleeding can be worsened by blood disorders involving the platelets (as in idiopathic thrombocytopenic purpura), coagulation mechanisms (as in VWD), or anticoagulant medication such as warfarin. Normal PT and aPTT do not rule out an underlying bleeding disorder, but they are adequate for screening for severe rare clotting factor deficiencies. However, these tests have poor sensitivity, specificity, and positive and negative predictive values for detecting an underlying bleeding disorder. Von Willebrand disease is the most common congenital human bleeding disorder, and is manifested by a quantitative deficiency in or dysfunction of VWF. It is more readily detected in woman because of the severe bleeding associated with menstrual periods and childbirth, but the frequency is actually the same in men and women. Clinically significant VWD occurs in a rate of 125 individuals per million, or 1–2% of the general population. In our study, of 482 women with menorrhagia 11.6% had inherited bleeding disorders and among them 55.3% had VWD. Type 3 VWD accounted for 45.2% of the cases, type 2 VWD consisted 32.3% and type 1 VWD accounted for the remaining 22.5%. The diagnosis of higher number of patients of type 3 VWD could be due to the fact that these patients were most severely affected and symptomatic; on the other hand, patients with type 1 VWD had mild symptoms, as a result lesser number sought for medical advice, leading to under diagnosis of milder type 1 VWD. The patients with type 1 VWD have mild bleeding episodes and hence consider their bleeding tendency as normal, unless they come across a major hemostatic challenge like trauma or surgery for which they get themselves investigated. These milder forms are often missed out on diagnosis or may not be detected at all as screening coagulation tests may be in the normal range. Because VWD is detected in many cases of women with menorrhagia, gynecologists recommend screening women for VWD. Dilley et al., reported that 10.7% women with menorrhagia had inherited bleeding disorders which among them 61.5% of these patients had VWD. In contrast, Vo et al. reported 9% women with bleeding disorders had VWD. Further, Borhany et al., reported 10.3% patients with a history of congenital bleeding disorders or suspected bleeding tendencies had inherited bleeding disorders. VWD was reported in 21.3% patients with inherited bleeding disorders. They reported type 3 was the most frequent with 51.4%, type 2 with frequency of 29.4% and lastly, type 1 with frequency of 19.1%.

Our study indicated a wide spectrum of clinical features of bleeding in participants. Common manifestation included mucocutaneous bleeds (37.8%), with gum bleeding, epistaxis, and bruises among these patients. We also had 8 patients with low VWF levels (30.92% ± 2.99 %), below the normal reference range. This category of patients, having low levels of VWF verses type 1 has been documented in the literature particularly in association with blood group “O”. Persons with very low VWF levels, <20 IU/dL, are likely to have VWF gene mutations, significant bleeding symptoms, and a strongly positive family history. But VWF levels of 30-50 IU/dL, just below the usual normal range (50–200 IU/ dL), pose problems for diagnosis and treatment.

CONCLUSION

In conclusion, our study showed that menorrhagia can be the first symptom of VWD as a rare coagulation disorders. Therefore, rare coagulation disorders should be considered in women with idiopathic menorrhagia, particularly in regions with high rates of consanguinity. A timely, accurate diagnosis may significantly increase the quality of care and management in these patients, and might also improve their quality of life and their reproductive history.

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