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ORIGINAL ARTICLE

Frequency and Clinical Spectrum of Von Willebrand Disease among Females with Bleeding Complaints at TCH-Hyderabad

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ABSTRACT

Background: Women with von Willebrand disease experiences more postpartum hemorrhage or the bleeding followed by surgery than the healthy women.
Aim: To determine the frequency of Von Willebrand disease among females presenting with bleeding complaints at tertiary care hospital. **Study Design:** Cross sectional study.
Methodology: Complete Blood Count, Bleeding Time, Prothrombin time, Activated Partial Thromboplastin Time were performed on the same day. Blood sample for CBC collected in EDTA tubes and for coagulation assays in tubes containing (3.2%) trisodium citrate. Von Willebrand's factor: Ag and Factor VIII were analyzed on Sysmex automated blood coagulation analyzer CA (600) while Ristocetin cofactor assay (RiCoF) was performed on Aggregometer. The collected data was analyzed by using SPSS version 25. Chi square ware applied with P-value< 0.05 as significant.
Results: Out of 80 patients, 56 patients were unmarried and 24 were married. VWD was found in 22/80 patients (27.5%). Type 3(50%) was the most frequent subtype followed by type2 (22.7%) and type 1(22.7%). In VWD, Menorrhagia (63.6%) was the most frequent symptom. APTT was prolonged in type3 VWD (50%). The mean VWF: Ag 18.5±20, VWF: RICOF 27.7±19 and factor VIII 74.9 ± 62.3 was noted in patients with VWD.
Conclusion: It was concluded that VWD is the most common inherited bleeding disorder in females presented with bleeding complaints. Awareness about the disorder is the need of time in order to prevent life threatening bleeding.
Keywords: Von Willebrand Disease, Menorrhagia and Bleeding Complaints.

INTRODUCTION

Von Willebrand disease (VWD) is the most frequent congenital bleeding disease. It is caused by quantitative or qualitative defect of von Willebrand factor (VWF), a plasma protein necessary in order to prevent bleeding.[1] VWD is divided into three major subtypes: type-1 VWD, type-2 VWD, and type-3 VWD. Type-1 VWD patients have a reduced plasma concentration of VWF, whereas type-3 VWD patients usually have an untraceable plasma VWF.[2] VWF is a large multimeric plasma protein, plays a significant role in primary hemostasis. When there is injury to blood vessel, endothelium is exposed to which Von Willebrand factor attaches with the platelets with the help of glycoprotein 1b. The other function of Von Willebrand factor is to protect factor VIII (FVIII) from its degradation[3].

In Pakistan, congenital bleeding disorders are common because of consanguinity and family marriages.[4] The most frequent symptoms in VWD patients are bleeding from nose, bleeding from mouth, hematomas, and bleeding followed by trauma/surgery. In women, menorrhagia is the main symptom leading to iron-deficiency anemia requiring oral or parenteral iron administration or allogeneic blood transfusions. The possibility of severe post-partum hemorrhage is amplified, especially in females with undetectable plasma factor levels in the last months of pregnancy. Most frequently, gastrointestinal bleeding is triggered by angiodysplasia, which is difficult to manage and diagnose[5].

To determine the severity of bleeding complaints, bleeding scores have been proposed. The ISTH (International Society on Thrombosis and Hemostasis) has structured a validated Bleeding Assessment Tool (BAT) for assessment of patients with VWD. Normal/abnormal values have been made for adult patients (males and females) and children. The ISTH BAT scores have been shown to correlate with the severity of VWD. ISTH BAT scores are more in type-3 VWD as compared to type-2 or type-1 VWD , and score is more significant in children with Type-3 VWD where levels of detectable VWF < 10 U/dL than children with VWD Type 1/VWD Type 2 where plasma VWF levels within range of 10-30 U/dL[6].

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Significant bleeding episodes that needs hospital admission, surgical involvement, blood transfusion for critical hemoglobin levels, bleeding including critical areas such as intracranial, intraocular and intra-spinal with compartment syndrome or repeated bleeding events that affects the daily life routine of the patients.[7] The study conducted in Karachi has reported the presence of VWD in 68 (21.3%) of 318 participants.[8] While another study taken out from India has reported the presence of the Von Willebrand disease in about 34.3% out of 200 participants.[9]
The importance of this study is that women with Von Willebrand disease experiences more postpartum hemorrhage or the bleeding followed by surgery than the healthy women so the early diagnosis of Von Willebrand disease help us to prevent life threatening complications.

The objective of the study was to determine the frequency of Von Willebrand disease among females presenting with bleeding complaints at tertiary care hospital**.**

METHODOLOGY

This study was conducted at department of pathology, Liaquat University of Medical and Health Sciences Jamshoro-Sindh. Females (n=80) with age ranging from 14 to35 years who presented with bleeding regardless of their marital status were enrolled. Complete Blood Count, Bleeding Time, Prothrombin time, Activated Partial Thromboplastin Time were performed on the same day. Blood sample for CBC collected in EDTA tubes and for coagulation assays in tubes containing (3.2%) trisodium citrate. Cleaned the venipuncture site with 70% alcohol swab. Tourniquet was applied for less than 1 minute. The needle were used 21 gauge for adults and for children 23 gauge. Blood was drawn into an EDTA for complete blood count, for coagulation tests, blood was drawn into sodium citrate collection tube (blue top).Fill to proper level. The blood was thoroughly mixed with anticoagulants by inverting gently six times, vigorous shaking was avoided. Blood sample for CBC collected in EDTA tubes were performed on Sysmex XN -1000. Blood was centrifuged to collect serum. Plasma Sample for VWF, Ristocetin cofactor and factor VIII were stored by making small aliquots of samples and were frozen at -65 Centigrade. Sample was thoroughly mixed after thawing at 37C,

repeated thawing and frozen was avoided. Von Willebrand's factor: Ag and Factor VIII were analyzed on Sysmex automated blood coagulation analyzer CA (600) while Ristocetin cofactor assay (RiCoF) was performed on Aggregometer. All women who were pregnant, having anti-platelet or Oral Contraceptive Pills, recent history of blood transfusion or factor concentrate with wash out period of 2 weeks were excluded.

Statistical analysis: Data was analyzed by using SPSS v.26. Qualitative parameters were presented as frequency. Mean and standard deviation was calculated for quantitative variable that are age, hemoglobin level, platelet count, PT, APTT, VWF: Ag, VWF: RCO and Factor VIII (FVIII). Post stratification chi square test was applied by taking p <0.05 or = 0.05 as significant.

RESULTS

Eighty patients were analyzed according to inclusion criteria for Von Willebrand disease in our hematology department. Out of 80 patients, 56 (70%) females were unmarried and 24(30%) females were married. VWD was present in 2(2.5%) married and 20(25%) unmarried females (Table 1). Out of 22 patients diagnosed as VWD, 18(81.8%) patients gave positive family history whereas 4(18.1%) patients do not give positive family history (Table 1).

Table 1: Comparison Of VWD With Marital Status & Family History (n=80)

VWD	Married (n=24)	Un-married V (n=56)	P-Value
Present	2 (2.5%)	20(25%)	0.012*
Absent	22(27.5%)	36(45%)	
	+ve family history	**-ve family History**	
Present	18	4	<0.001*
Absent	13	45	

*Statistically significant

Almost 58 patients (72.5%) with bleeding complaints presented at young age group (14 to 20 year), 13(16.25%) patients were presented at age of 21-25years and 9(11.2%) patients were presented at age group (26-30 year) as shown in table-2.

Table-2: Frequency of Females with Bleeding Complaints with respect to Age

Age (years)	VWD present (n=22)	VWD absent (n=58)
14-20	17(21.2%)	41(51.2%)
21-25	04(05%)	09(11.2%)
26-35	01(1.2%)	08(10%)

P value 0.3

Out of 80 patients, 35 females (43.7%) presented with complain of menorrhagia since menarche where p value was significant p=0.02, females presented with nasal bleed (n=12), oral cavity bleeding (n=5), post dental extraction (n=3), Gastrointestinal bleeding (n=3), post-surgery bleeding (n=4), postpartum hemorrhage (n=3) and 15 females presented with bleeding from multiple site (include nasal bleed, oral bleeding, post dental extraction, GI bleeding) (Table 3).

Table 3: Clinical features of patients presented with VWD and without VWD

Symptoms	VWD present	VWD absent	P-value
Nasal Bleeding (n=12)	0	12(15%	-
Oral Bleeding (n=5)	0	05(6.25%)	-
Post-dental extraction (n=3)	0	03(3.75%)	-
GI-bleeding (n=3)	0	03(3.75%)	-
Post-surgery bleeding (n=4)	0	04(5%)	-
Menorrhagia (n=35)	14(17.5%)	21(26.2%)	0.02*
Postpartum bleeding (n=3)	0	03(3.75%)	-
Bleeding from multiple sites (n=15)	08(10%)	07(8.75%)	0.83

*Statistically significant

Type 3 was the most frequent subtype of VWD. It was present in 11 (50%) patients out of 22 patients, type2 was found in 5/22 (22.7%) patients and type 1 was found in 5/22 (22.7%) patients. 1/22 patient (5%) was found to have low VWF (Table-4).

Table-4: Frequency and percentage of subtype of VWD (n=22)

Type of VWD	n	%age
Type1 VWD	05	22.7%
Type2 VWD	05	22.7%
Type3 VWD	11	50%
Low VWF	1	4.5%

Table-5 showed mean and standard deviation of various parameters of patients presented with bleeding complaints. In VWD, the mean age was 17.3 years. The mean hemoglobin level was 7.8g/dl. Platelet count was normal in all patients with Von Willebrand disease with mean platelet count 361.1x109. PT was normal in all females. The mean VWF: Ag 18.5±20, VWF: RICOF 27.7±19.1 and factor VIII 74.9±62.3 were noted in patients with VWD.

Table-5: Bleeding Complains Presented as Mean ± SD

Variables	MEAN ± SD
Age (years)	18.4 ± 5.2
Hemoglobin (g/dl)	8.7 ± 2.4
Platelets (x 10^9)	315.2 ± 144
APTT (sec)	31.3 ± 7.8
VWF: Ag (%)	91.3 ± 57.5
VWF:RICOF (%)	91 ± 50.2
Factor VIII (%)	115 ± 50.3

DISCUSSION:

Low VWF usually considered when VWF level is between 30-50%. Our data showed 22 out of 80 (27.5%) patients diagnosed as VWD presented with various bleeding complaints. Type-3 was the most common type of VWD present in 11 (50%) patients out of 22 patients, type-2 in 5 (22.7%) patients and type-1 was present in 5(22.7%) patients. One (1.25%) patient was having low VWF. The Differentiation between Type 1 and type 2 depends upon ratio of VWF Ricof/Ag, if ratio is>0.6 then it is labeled as type-1 VWD and if ratio is <0. 6 then it is labeled as Type-2 VWD.

VWD type 3 is autosomal recessive disorder. In my study, most common type of VWD is type 3 (50%). One study from Karachi, Arshi Naz et al concluded that type 3 VWD (33.8%) was common among autosomal recessive disorder in Pakistan[10].

In another study, one researcher reported that VWD type-3 is occurring in 95 patients (33.5%) whereas VWD type-1 and type-2 is found in 11(3.88%) patients[11]. The higher number of type-3 VWF could be due to severe deficiency of VWF factor and factor VIII that causes major bleeding episodes and patients usually seeks medical attention. On the other hand, patients with Type-1 VWD had mild bleeding symptoms due to which lesser number of patients seeks medical advice. Type-1 VWD was seen in 05/22 (22.7%) of patients in our study in contrast to higher prevalence of this type in other countries such as one study from Oman, 140 diagnosed patients with VWD, 66 patients have type-I (47%), 38 patients have type II (27%) and 36 patients have type-III (26%)[12].

The patients with type-1 VWD experiences major bleeding when there is trauma or surgery otherwise they experience mild bleeding symptoms. In one study from Karachi, showed frequency of 21.3% of VWD with type 3 was most common subtype with frequency of 51.4%, type 2 with frequency of 29.4% and type 1 with frequency of 19.1%[8].

In one study conducted at Thailand, Type 2(48.2%) was the most common type of VWD and the majority of them were type-2A.[13] In our study, there was positive family history in 18 patients out of 22 diagnosed as VWD. Detailed family history plays important role in investigating patients with bleeding symptoms as consanguineous marriages are common in Pakistan[4]. Our study showed wide range of signs and symptoms in our patients. Multiple sites involved bleeding from mouth and nose, gastrointestinal

bleeding, menorrhagia, major bleeding followed by surgery or trauma and postpartum hemorrhage. Menorrhagia was most common symptom observed in females (35/80) due to which female patients seek medical Advice. It has been observed that bleeding disorders, specifically von Willebrand disease (VWD) and platelet function (PFD) disorders, are more present in women with menorrhagia[14]. In our study Out of 35 females presented with menorrhagia, 14 females are diagnosed for VWD. In our study and other studies from Pakistan, menorrhagia was main symptom among female patients[8]. 20/22 patients were unmarried as VWD is more commonly diagnosed in young females presented with excessive menstrual loss at the age of menarche so first line investigation for VWD should be done in females presenting with menorrhagia. In our study, apart from mucocutaneous bleeding, two patients experienced hemarthrosis and hematomas due to severe Factor VIII deficiency. Three patient had history of postpartum hemorrhage but none of the patient was diagnosed as VWD in our study. In our study, platelet count was normal in all patients of VWD however Type 2 b can be presented with low platelet count. APTT was raised in 13/22 patients in VWD due to deficiency of factor VIII along with VWF:Ag and Ricof level. APTT was more prolonged in type 3 VWD as VWF is almost deficient in these patients.

Limitations: It was a single centre study and we did not perform genetic workup among patients in-order to find the genetic cause. There was less follow-up and it was carried out on small sample size.

CONCLUSION

It was concluded that VWD is the most common inherited bleeding disorder in females presented with bleeding complaints. Awareness about the disorder is the need of time in order to prevent life threatening bleeding. Majority of cases of VWD remain undiagnosed due to various clinical features and confounding weaknesses in laboratory diagnosis. Comprehensive assessment of patients, followed by careful laboratory testing is necessary to diagnose VWD.

Author's contribution: SK&NUAA: Conceptualized the study, analyzed the data, and formulated the initial draft, **NM&IDU:** Contributed to the proof reading, **M&SK:** Collected data.

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