Clinical Spectrum and Laboratory Study of Von Willebrand Disease -Experience from Tertiary Care Hospital in Pakistan

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ABSTRACT

Objective: To determine the clinical features and laboratory parameters of patients of von Willebrand disease (vWD) in our population.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Hematology, Armed Forces Institute of Pathology (AFIP), Rawalpindi Pakistan, from Jan to Jul 2019.

Methodology: All patients newly diagnosed von Willebrand disease patients were assessed clinically. Complete blood counts, bleeding time, coagulation profile, von Willebrand antigen levels and FVIII levels were determined.

Results: A total of 66diagnosed patients of von Willebrand disease were included in the study. Out of these 15 (22.7%) were male while 51 (77.2%) were females. The most common clinical symptom was pallor, seen in 49 (74.2%) patients, followed by epistaxis in 36 (54.5%) and gum bleeding in 28 (42.4%) patients. Consanguineous marriages were found in 40 cases (60.6%) and family history was positive in 23 (34.8%). Patients mean vWF Ag level was4.29 ± 7.7 IU/dL while mean FVIII levels was 5.18 ± 7.8 1 U/mL.

Conclusion: Von Willebr and disease is among the most common inherited bleeding disorder which presents with a classical pattern of mucocutaneous/soft tissue bleed, with pallor epistaxis and gum bleed being the most common presenting complaints.

Keywords: Bleeding time, Factor viii, Inherited, Von wille-brand disease, Von wille-brand antigen.

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INTRODUCTION

Erik von Willebrand in 1926 described an inherited bleeding disorder and characterized it as pseudo hemophilia.[1] Von Willebrand factor is the missing agent responsible for the pathogenesis of this disease as it binds to collagen at the site of injury mediating aggregation and adhesion of platelets and serving as a carrier for coagulation factor VIII.[2]

Epidemiological studies regarding von Willebrand disease (vWD) suggest a prevalence of 0.6-1.3%.[3] It is classified into three types based on the qualitative and quantitative defects of von Willebrand factor. Type-I is characterized by a partial quantitative deficiency of von Willebrand factor and is present in 70-80% cases. Type-II accounts for 20% of cases caused by dysfunctional vWF, resulting in reduced concentration of von Willebrand factor antigen levels. Type-III is rare (accounting for 5% cases) and is caused by complete absence of circulating von Willebrand factor. Type-II is further sub classified into four subtypes (Type 2A, 2B, 2M, 2N) based on the pathophysiology.[4]

Given the multifaceted nature of the illness, the capacity to precisely diagnose and determine people suffering from Von Willebrand Disease keeps on being a significant and much talked about subject. Diagnosis of von Willebrand disease is based on three main criteria including history of bleeding, family history of bleeding and decreased levels of vWF. However, diagnosis is difficult due to lack of standardization, assay and cutoff variability.

Classical pattern of mucocutaneous bleeding is observed in this disease with epistaxis, gum bleed and easy bruisibility among the most common presenting complaints.[5] Clinically evident bleeding in von Willebrand disease can range from spontaneous bleed or caused by mild activity to that caused by a trauma or a surgical procedure. Type-III patients usually exhibit a bleeding pattern similar to hemophilia A or B due to frequent episodes of hemarthrosis and deep muscular hematomas.[6]

Two von Willebrand factor specific laboratory tests being used to diagnose this disease are measuring

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the quantity of vWF in plasma and its efficacy to bind the platelets in the presence of antibiotic ristocetin.[7] Along with vWF activity assay factor VIII assay is also carried out for accurate differentiation and categorization of patients into vWD Type-I, II and III.

Rare bleeding disorders usually constitutes upto 3-5% of all the inherited coagulation defects.[8] Accurate differentiation of vWD from the rare bleeding disorders is essential for early diagnosis and prompt treatment of this commonly occurring condition. The aim of this study was to identify the clinical spectrum and laboratory parameters associated with vWD in our population in order to facilitate its early recognition and diagnosis.

METHODOLOGY

This cross-sectional study was conducted at the Department of Haematology, Armed Forces Institute of Pathology (AFIP), Rawalpindi Pakistan, from January to June 2019. AFIP is a tertiary care referral centeroffering specialized diagnostic facilities to patients from different parts of the country. A sample size of 20 was calculated using WHO sample size calculator 3, with prevalence of 1.3% and confidence level of 95%, however 66 samples were included in our study. A non-probability consecutive sampling criteria was used. Patients who were newly diagnosed cases of von Willebrand disease of either gender irrespective of age were inducted in the study. Patients with other bleeding disordersor an acquired cause of bleeding were excluded from the study.

After taking permission from the ethical committee review board(Ref No. FC-HEM 117-34/ READ-IRB/399 Dated 07 Aug 2018), written informed consent was taken from the patients. Patient particulars, history of consanguineous marriage and positive family history of bleeding were endorsed in the proforma. Clinical features including pallor, history of easy bruisability, gum bleed, menorrhagia, epistaxis, hematuria, melena, circumcisional bleed, hemarthrosis, bleeding from the umblical cord and jaundice were recorded. History of RCC or FFP transfusion was also noted.

Two and a half ml of blood was taken via venipuncture in the EDTA tube and platelet count was performed using automated analyzer Sysmex XE-5000. Bleeding time was assessed using IVY method. For assessment of coagulation profile (prothrombin time (PT), partial thromboplastin time (PTTK) and thrombin time (TT) venous blood was taken into trisodium citrate tube in a ratio of 9:1.After preparation of platelet poor plasma, automated analyser (sysmex CA-1500) was used to analyse the coagulation profile of each sample. Quantitative determination of vWF antigen levels was done on automated coagulation analyzer CA-1500 by immunotubidimetry. Clotting based one stage factor VIII bioassay was performed using Siemens factor VIII deficient plasma on automated coagulation analyzer CA 1500.

Data was analysed using SPSS version 25.0. Mean and SD was calculated for numerical variables such as age, platelet count, vWF antigen levels, factor VIII assay activity levels. Percentage and frequency was calculated for categorical variables like gender, pallor, history of bruisability, gum bleed, menorrhagia, epistaxis, hematuria, melena, circumcisional bleed, hemarthrosis, bleeding from the um-blical cord, jaundice and history of RCC and FFP transfusion.

RESULTS

A total of 66 newly diagnosed patients ofvon Willebrand disease were enrolled for our study. Out of these 66 patients, 15 (22.7%) were males and 51 (77.3%) were females. Mean age of the patients was 7 ± 6.93 years. Minimum age of the patients observed was 0.24 years and maximum was 26 years.

History of consanguineous marriage was present in 40 patients accounting for 60.6%. Majority of the patients 43 (65.2%) in our study showed a negative family history of bleeding disorder. Only 23 (34.8%) patients screened had a positive family history for bleeding disorders (Table).

Table: Family history and consanguinity in our study population.

	Positive	Negative
Family history	23 (34.8%)	43 (65.2%)
Consanguineous marriage	40 (60.6%)	26 (39.4%)

Coagulation studies revealed that bleeding time (BT) of 59 (89.4%) patients was increased and recorded to be more than 15 mins and 55 (83.3%) patients had a bleeding time of less than 15 mins. PT was normal (14/14) in all the patients and PTTK had a mean value of 53/32 with the highest value of 69/32 and lowest value of 32/32. 9 out of 66 patients showed a very high level of PTTK. Mean of vWF antigen levels was 4.29 ± 7.7% IU/dL and factor VIII assay was 5.18 ± 7.8% U/mL . Platelet count had a range of 261-711 $x10^3$ /µL with a mean of 409.5 ± 109.3 $x10^3$ /µL.

Most frequently observed symptomsat the time of presentation were pallor 49 (74.2%), gum bleeding 28

(42.4%) and epistaxis 36 (54.5%). The other less commonly occuring symptoms observed were hematuria 6 (9.1%), melena 4 (6.1%), menorrhagia 15 (22.7%), easy bruisibility 23 (34.8%), circumcisional bleed 7 (10.6%), hemarthrosis 21 (31.8%) and bleeding from the umbilical cord 16 (24.8%). 11 out of 66 patients required FFP transfusion and 18 out of 66 patients received RCC transfusion.

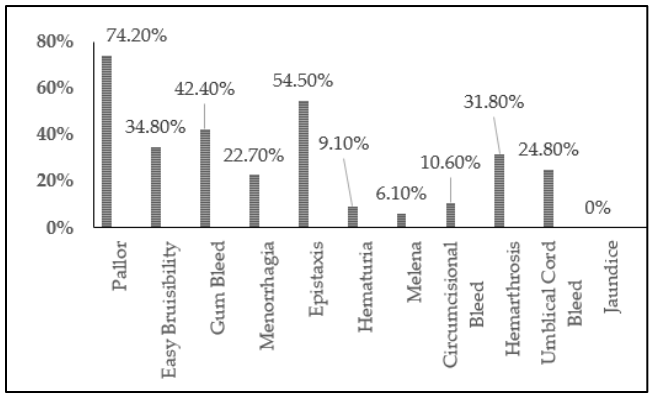

Figure: Symptoms associated with von.

DISCUSSION

The presence of clinical manifestations in von Willebrand disease are mild in Type-I and its severity increases in Type-II and III. Type-I is classified as a monongenic dominant trait. The most common and well researched genetic modifier for this condition is the ABO blood grouping. Patients with type O blood group demonstrates the vWF levels less than 25% of the normal as compared to Non O groups, thus its coinheritence is considered to play a major pathogenic role in the von Willebrand type-I disease progression.[10]

Autosomal pattern of inheritance of vWD suggests an equal distribution of male and female patients. However, our study revealed a gender predilection towards female with a male to female ratio of 1:3.4. This is in accordance with the systematic review conducted by Meena *et al,* which showed an overall prevalence of 0.8-1.3% in general population with a greater prevalence in females.[11] Quantitative analysis by A. Tosetto *et al,* revealed a 55% female population affected by Type-I von Willebrand disease.[12]

Family history was positive in 23 (34.8%) patients out of 66. Shahida *et al,* reported that 60% population affected with vWD had a positive family history of either a rare bleeding disorder or hemophilia A.[13] In our study history of Consanguineous marriages were positive in 40 patients out of 66 that accounted for a large percentage of 60.6% which is one of the significant finding. Shahbazi *et al*, also reported that majority of the patients in Iran were born as a result of consanguinity.[14] An analysis of Northern Pakistani population revealed a 40.6% of the consanguineous marriages in the patients affected by vWD.[15]

A wide range of bleeding manifestations was found in the patients of vWD. Pallor (74.2%), gum bleed (42.4%) and epistaxis (54.5%) were the most commonly reported symptoms in our study population. A study conducted by an indian author suggested von Willebrand as a hybrid disease showing symptoms similar to that of platelets and coagulation factor deficiency with mucocutaneous bleeding (epistaxis, gum bleed, ecchymosis) more common than coagulation type bleeding like hemarthrosis and hematomas etc. Sanders *et al,* showed similar results with epistaxis and bruising being the most frequently presenting symptom in children.[16] In adults the most prevalent symptoms were hematoma, menorrhagia and bleeding from minor wounds. Other less commonly accounted symptoms included easybruisibility (34.8%), hemarthrosis (31.8%), bleeding from the umblical cord (24.8%), circumcisional bleed (10.6%), hematuria (9.1%) and melena (6.1%). Similar prevalence has been reported by Nicholas *et al,* and Veyradier *et al*, in their studies.[17,18]

Menorrhagia (overall 22.7%), was found in 100% of females of reproductive age group in our study sample. Balkan *et al,* conducted a study in turkey and concluded that 55% of the females affected with vWD, had menorrhagia. When further evaluated, Out of these 69% were type-I, 17% were Type-II and 14% were Type-III.[19] The underlying cause of menorrhagia in 5-20% of women reporting to the clinicians is usually von Willebrand disease.

Phenotypic analysis is sometimes sufficient for discerning the type of vWD, however, in some patients this does not suffice the requirements and genetic analysis is needed for further categorization. PCR and sanger sequencing have been the mainstay of genetic analysis for several decades. However next generation sequencing has revolutionized the face of genetics aiding in specific typing and characterization of vWD.[20]

Normalizing the levels of von Willebrand factor and factor VIII in case of bleeding episode or before any minor surgical intervention is the aim of treatment in management of patients with vWD. This can be achieved by raising the endogenous levels of factor or infusion of exogenous factors of coagulation. Recent Advancements in factor replacement treatment for

patients with VWD has increased the paradigm of treatment options. This poses a test for a standard calculation of dosage, however may help conquer the impediments of prior medications and permit treatment personalization as per singular patient needs.

CONCLUSION

Von Willebrand disease is the most common inherited bleeding disorder which presents with a classical pattern of mucocutaneous/soft tissue bleed. Its differentiation from rare bleeding disorders and hemophilia is of paramount importance in order to start early treatment and avoid any major hemorrhagic episode thus improving the quality of life of an individual.

Conflict of interest: None.

Author's Contribution

MH: Direct contribution to conception, design, analysis, interpretation, AM: Data analysis, RM:, NS: Intellectual contribution to analysis and interpretation, AK: Manuscript preparation, NK: Data collection.

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