

ORIGINAL ARTICLE

SPECTRUM OF VON WILLEBRAND'S DISEASE IN PUNJAB: CLINICAL FEATURES AND TYPES

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Background: Von Willebrand's disease (VWD) is a common inherited bleeding disorder caused by quantitative deficiency (Type-1 & Type-3 VWD) or qualitative defect of Von Willebrand's Factor (Type-2 VWD). Regarding VWD limited studies are available in Pakistan. The current study was aimed to determine the clinical presentation and frequency of types of VWD. **Methods:** A cross sectional study was carried out from 16th December 2012 to 15th December 2013 on fifty one patients of VWD. **Results:** Patients were diagnosed on the basis of prolonged bleeding time, abnormal APTT, reduced level of VWF: Ag, FVIII, VWF: RCo and ratio of VWF: RCo/VWF Ag. Among them 26 (50.98%) were male and 25 (49.02%) were female. Type3 VWD (94.12%) was found to be the commonest type. Two (3.92%) cases of type-2 VWD and only one (1.96%) case of type-1 VWD were identified. Easy bruising was the most commonly observed clinical presentation, 21 (41.18%) patients, followed by epistaxis 7 (13.73%), gum bleed 4(7.84%) menorrhagia 5(9.80%), haemarthrosis 2(3.92%), haematoma formation 5 (9.80%), bleeding after circumcision 2 (3.92%), bleeding after surgery 2 (3.92%) and umbilical cord bleeding 3 (5.88%). Consanguineous marriages were reported in parents of 42 (82.4%) patients. Family history of bleeding disorder was reported in 44 (86.27%) of cases. **Conclusion:** Type-3 VWD was found to be the commonest type which can be attributed to the fact that type-3 VWD is transmitted through autosomal recessive pattern of inheritance and consanguineous marriages are highly practiced in our society leading to high frequency of this form of VWD. Easy bruising and epistaxis were concluded to be the most common clinical presentation. Menorrhagia was found to be common in the females of child bearing age.

Keywords: von Willebrand disease. Bleeding time. Ratio of VWF: RCo/VWF Ag

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INTRODUCTION

Von Willebrand's disease (VWD) is a common inherited bleeding disorder caused by a quantitative deficiency or qualitative defect of von Willebrand factor (VWF).¹ Prevalence of VWD is about 1% of normal population throughout the world but prevalence of its different types is not known in Pakistan.² Both gender have been found to be affected equally by the disease.³

The disease was first described by Dr Erik von Willebrand in 1926 in the Åland Archipelago.⁴ The disease is caused by the quantitative deficiency or dysfunction of VWF, a large multimeric glycoprotein⁵ that is encoded by a gene spanning 178 kb of genomic DNA on chromosome-12.^{6,7} The gene product is a 2813-amino-acid polypeptide, consisting of a 22-amino-acid signal peptide and a 741-amino-acid propeptide that is cleaved during intracellular processing, resulting in a mature subunit of 2050 amino acids. VWF is synthesized by the endothelial cells and megakaryocytes and is stored in Weibel-Palade bodies and alpha granules.^{8,9} VWF has two main functions; firstly it helps in platelet plug formation after a vessel injury and second is that it works as a protective carrier of FVIII. Thus any defect or deficiency of VWF leads to defective platelet plug formation and fibrin formation.

Most common clinical presentation of VWD includes epistaxis and menorrhagia. Besides these the patient of VWD also presents with gum bleeding, easy bruising and prolong bleeding after surgery. Type-3 VWD patients or severely affected patients present with haemarthroses like Haemophilia.^{10,11}

VWD is diagnosed on the basis of prolonged bleeding time, abnormal APTT, low plasma levels of Factor-VIII, low plasma level VWF antigen and or abnormal VWF antigen, Ristocetin induced platelet aggregation, Ristocetin cofactor activity¹² and multimeric analysis of VWF protein.^{13,14}

Patients of VWD need lifelong treatment and treatment plan is made by typing of the disease because each type has separate treatment option. The ratio of Ristocetin Cofactor Activity to VWF Antigen is used for differentiating type-1 and type-2 VWD. Type-3 VWD is confirmed by undetectable to less than 10 IU/dL VWF protein with markedly decreased activity and FVIII level ranging from 1 to 9 IU/dL.2 The VWF:RCo has some limitations in disease typing, that it has high inter-laboratory and intra-laboratory variations and does not actually measure the physiological functions. Without performing multimer analysis of VWF protein, this ratio is still most widely accepted for differentiating type-1 from type-2 VWD.

Multimer analysis of VWF protein is a specialized test, used for diagnosis and typing of VWD.⁵

Desmopressin and oral contraceptives are used in mild cases of VWD.^{4,15} Humate P and Alphanate (FVIII/VWF concentrates) are required for treatment of severe cases of VWD.¹⁵ Cryoprecipitate and fresh frozen plasma contains are transfused in emergency cases only as these agents are responsible for transmission of viral infections.¹⁵

Regarding VWD very limited studies are available in our country. Information about frequency of VWD is available which reveals that type-3 VWD is the commonest type.¹³ The present study was designed to find out clinical presentations and frequency of different types of VWD in Punjab population.

MATERIAL AND METHODS

This cross sectional study was carried out in the Department of Pathology, Postgraduate Medical Institute Lahore in collaboration with Pakistan Haemophilia Patients Welfare Society, Lahore from 16 December, 2012 to 15 December 2013. Five hundred and ten patients registered with Pakistan Haemophilia Patients Welfare Society were included in the study. Each patient was informed about the study individually and written consent was taken from all adult patients. Written consent of the children was taken from their legal parents/guardians. Personal information of patients were recorded on the predesigned *pro forma* designed for the study. The records of all the patients were reviewed. The patients with prolonged bleeding time and abnormal APTT of all ages, gender and ethnic groups were included. Patients with bleeding disorders other than VWD, liver disease, kidney disease, patients having recent history of drug intake e.g., anti-platelet drugs, Heparin, Warfarin, Clopidogrel, oral contraceptive pills, recent history of blood transfusion, transfusion products or clotting factor/VWF concentrates with washout period of less than one week and pregnant females were excluded from the study.

Two samples of venous blood of each patient were collected. One sample was collected in an Ethylene diamine tetra-acetic acid (EDTA) vacutainer tube. The second sample was collected in 3.2% trisodium citrate vacutainer tube and had exactly 9 parts of blood and 1 part of anticoagulant. Samples were examined with naked eye for haemolysis, bubbles and clots. Patients' Platelet Poor Plasma was prepared by centrifuging at 2000–3000 x G for 15 minutes. APTT was performed soon after making platelet poor plasma. The remaining plasma was stored frozen in plastic tubes at -30 °C for specialized tests for two weeks. The stored plasmas were thawed quickly at 37 °C before testing.

The data was analysed using SPSS-20. Quantitative variables were given as mean \pm Standard deviation and categorical variables were shown as frequencies and percentages.

RESULTS

Family history for bleeding tendency was determined by interviewing each patient. Among them forty four patients (86.27%) presented with positive family history of bleeding disorder, while seven patients (13.73%) showed no family history of bleeding disorders.

Consanguinity was reported in forty two patients (82.35%) and nine patients (17.65%) showed no history of consanguinity. Twenty-five patients (49.02%) were female and 26 patients (50.98%) were male. Type-3 VWD was observed in 48 patients (94.12%), type-2 VWD was seen in 2 patients (3.92%) and type-1 VWD was identified in only one patient (1.96%).

Easy bruising was the most common presenting feature in these patients, which accounted for 21 (41.18%), followed by epistaxis 7 (13.73%), gum bleed 4 (7.84%), menorrhagia 5 (9.80%) among adult females, haemarthrosis 2 (3.92%), umbilical cord bleeding 3 (5.88%), bleeding after circumcision 2 (3.92%), bleeding after surgery 2 (3.92%), and haematoma in 05 patients (9.80%) as shown in figure 1. All patients were grouped according to their age groups. Age group 1–6 years comprises 11 patients (21.57%), age group 7–12 years consists of 8 patients (15.69%) and patients of 13 years and above comprise 32 (62.75%).

Mean and SD value for all parameters used for diagnosis and typing of VWD are described in table-1. The numerical variables were determined in all patients of VWD. Bleeding time was performed and it was more than fifteen minutes in all patients of VWD, so mean \pm standard deviation was not calculated for this variable.

In all patients of VWD, platelet count was determined. Mean platelet count type-1 VWD and was 166 \pm 0. In type-2 VWD it was 195 \pm 8.5, and in type-3 VWD it was 336.25 \pm 111.4. Mean APTT in type-1 VWD was 58 \pm 0 Sec. In type-2 VWD it was 55 \pm 1.41 Sec, and in type-3 VWD it was 65.33 \pm 11.3 Sec.

In all patients of VWD, Factor VIII was below normal range. Mean value of FVIII in type-1 VWD was 9.400 \pm 0%, in type-2 VWD it was 7.750 \pm 0.21 % and in type-3 VWD it was 2.946 \pm 2.486 %. Mean VWF:Ag in type-1 VWD was 23.700 \pm 0%, in type-2 VWD it was 12.650 \pm 1.91% and in type-3 VWD it was 1.010 \pm 0.476%.

Ristocetin cofactor activity was determined in all patients. Mean RiCof level in type-1 VWD was

19.09±0%, in type-2 VWD it was 6.1400±0.9334% and in type-3 VWD it was 4.392±3.880%.

The ratio of Ristocetin cofactor activity to VWF antigen was calculated as shown in table2. In one patient it was 0.81 (more than 0.7), and the patient was labelled as type-1 VWD. In two patients the ratio was 0.39 and 0.58 (less than 0.7), and these two patients were labelled as type-2 VWD. In rest of the 48 patients the ratio was not applicable since VWF:Ag value was less than 10% and these patients were typed as type-3 VWD.

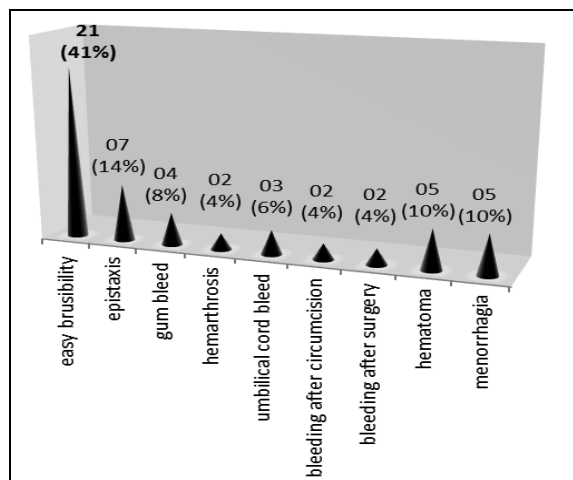


Figure-1: Clinical presentation of patients.

Table-1: Parameters of different types of VWD

	Type-1 VWD (n=1)	Type-2 VWD (n=2)	Type-3 VWD (n=48)
APTT	58.00±0	55.00±1.41	65.33±11.31
Platelet count	166.00±0	195.00±8.49	336.25±111.39
Factor VIII	9.400±0	7.75±0.21	2.95±2.49
VWF:Ag	23.70±0	12.66±1.90	1.01±0.48
RiCof	19.09±0	6.14±0.93	4.39±3.88

Table-2: Types of VWD

RiCof/VWF:Ag Ratio	Type-1 VWD n=1	Type-2 VWD n=2	Type-3 VWD n=48
Result	0.81	0.39 and 0.58	Not Applicable
Cut off value	> 0.7	< 0.7	-

DISCUSSION

Consanguinity is highly practiced in our society, resulting in high frequency of autosomal recessive type-3 VWD. Consanguinity was reported in 82.4% in the present study and in a study by Shahbaz *et al.*, 40.6% consanguineous marriages were observed in parents of patients of VWD.¹ Hussain *et al* reported this value as 58.7% in Karachi while 62.7% by Pakistan Demographic and Health Survey.¹⁶ One of the reasons of high frequency of type-3 VWD in our population may be due to the fact that consanguineous marriages are highly practiced in our society.

Family history for bleeding tendency was detected in 86.27% of the patients in the current study.

Results of the present study were similar to the study by Zhang *et al.*, who stated that 60% patients presented with positive family history of bleeding disorder.¹⁷ Woods *et al.*, identified 56.9% patients and Borhany *et al.*, showed 72.0% patients.^{2,18} Trasi *et al.*, reported 29.31% with positive family history for bleeding tendencies, which was quite low as compared to the present study.²¹

Similar observations were made from studies conducted in northern part of Pakistan and Karachi. Shahbaz *et al.*, also reported type-3 VWD to be the most common type.¹ Borhany *et al.*, reported type-3 VWD to be 51.4%, type-2 VWD as 29.4% and type-1 VWD as 19.1%.² Trasi *et al.*, is of the opinion that type-3 VWD is as common as 59.5%, type-2 VWD 19% and type-1 VWD 18%.²¹

In the present study easy bruising was the most common presenting complaint, followed by epistaxis, gum bleed, menorrhagia among adult females, haemarthrosis, umbilical cord bleeding, bleeding after circumcision, bleeding after surgery and haematoma. Zhang *et al.*, reported epistaxis and easy bruising as the most common clinical symptoms in their patients.¹⁷ Federici, reported some of symptoms in Iranian population of type-3 VWD, which were the same as in the current study.¹⁵ Federici stated the symptoms as epistaxis 77%, menorrhagia 69%, post extraction bleeding 70%, post-surgical bleeding 41%, joint bleeding 37%, GI bleeding 20%, postpartum bleeding 15% and hematuria 1%.¹⁵ In 2004 Federici stated that mucosal bleeding was the most frequent clinical presentation i.e., 64% and haematoma or hemarthrosis was reported to be 15%.¹²

Slightly different statistics were presented by Woods *et al* in 2001. According to him ecchymoses and hematoma were the commonest symptoms presented by the patients, accounting for 50.4%.¹⁸ These symptoms were followed by menorrhagia 47.0% in females of reproductive age, epistaxis 38.1%, gum bleed 26.1 %, bleeding after tooth extraction 28.6%, bleeding after surgery 19.5%, post-partum haemorrhage 12.9%, hemarthrosis 6.3% and hematuria 4.7%.¹⁸

Favaloro *et al* in 2000 and 2004 emphasized that VWD is diagnosed and its typing is done on the basis of FVIII level, VWF:Ag assay, RiCof activity and ratio of RiCof to VWF: Ag without performing VWF multimer analysis.^{19,20} They are of the opinion that Factor-VIII, von Willebrand factor antigen and either/or both von Willebrand factor ricof (VWF:RCo) and von Willebrand factor collagen binding assay (VWF:CB) can be used to diagnose or classify VWD without performing VWF multimer analysis.^{19,20}

CONCLUSIONS

Type-3 VWD was found to be the commonest type in Punjab population. Since type-3 VWD is transmitted through autosomal recessive pattern of inheritance and consanguineous marriages are highly practiced in our society, hence it may be the cause of high frequency of severe form of VWD. Easy bruising and epistaxis were the most common clinical presentations of patients of VWD. Menorrhagia was found common in females of child bearing age. Due to unawareness of the disease, varied clinical presentation, referral of only symptomatic patients to tertiary care hospitals and lack of proper diagnostic facilities most of the mild cases of VWD remain undiagnosed in Pakistan.

RECOMMENDATIONS

Studies need to be carried out based on VWF multimer and genetic analysis, so that mutations responsible for VWD can also be recognized in our local population. Families with bleeding disorders should be screened on a larger scale, so that mild forms of the disease can also be detected.

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