Original Research Article

Analysis of clinical and laboratory characteristics in patients with von Willebrand disease in a five year follow up at a tertiary referral centre in Sri Lanka

ABSTRACT

Background- von Willebrand disease (vWD) is the commonest, inherited bleeding disorder worldwide. A retrospective cross-sectional study was done to analyze clinical and laboratory characteristics in 47 diagnosed patients with vWD and to assess the utility in basic bleeder screen and BAT(Bleeding Assessment Tool) score in a five year (2012-2017) follow up at a tertiary referral centre in Sri Lanka.

Method- Clinical assessment was done by using the BAT score. Initial screening tests of coagulation profile and bleeding time was analyzed. Ristocetin Induced Platelet Aggregation (RIPA), vonWillebrand-antigen, activity and Factor-VIII were also done to confirm and categorize the subtype of the disease.

Results–The commonest type was type 1 (31, 70.2%) followed by type 2B/Platelet type (8, 17%) and type 3 (8, 17%). Type 3 disease showed the highest average BAT score followed by type 2B disease which is compatible with their bleeding severity. Bleeding time was prolonged in 21(44.7%) and was normal in 26 (55.3%) of patients. APTT was prolonged in only 31(66%) and was normal in 16 (34%). A positive family history was seen in 27 (57.4%), negative family history in 17 (36.2%) patients and family history was unknown in 3(6.4%) patients. Type 3 and Type 1 VWD patients showed a higher association with a positive family history.

Conclusion-In the diagnosis of vWD, the basic bleeder screening tests alone are not enough and using BAT score incorporated with family history showed to be more useful. Therefore, combining both these will provide a better bleeder screening method for the vWD.

Keywords: von Willebrand disease, BAT score

1. INTRODUCTION

von Willebrand disease (vWD) is the most common inherited bleeding disorder with a prevalence of 1-2% based on population studies. [1]
It was described almost a century ago (1926), and still remains as a complex bleeding disorder. There is a qualitative or quantitative defect in the von willebrand factor (vWF),

mainly with autosomal dominant inheritance, resulting in defects of both primary and secondary haemostatic mechanisms. [2]

There are more than 250 vWF genetic mutations identified which are associated with all the types of vWD. There are three main types in vWD, Type 1,Type 2(2A,2B,2N,2M) and type 3[3]. Type 1 is an autosomal dominant disorder caused by a partial quantitative deficiency of vWF[4]. The structure and the distribution of plasma vWF multimers are indistinguishable from the normal factor. Type 2 is a qualitative defect of vWF with type A,B, and M having an autosomal dominant inheritance [5] .Type 2A is caused by a missense mutation within the vWF while type 2B is caused by reduced high molecular weight multimers. Type 2M is caused by specific defects in platelets. Type 2N is autosomal recessive caused by defective vWF binding to F VIII and low levels of circulating F VIII. Type 3a is clinically severe, quantitative disorder. It is autosomal recessive, caused by markedly reduced or absent platelet and plasma vWF.[1][6][7][8][9]

According to the literature, the prevalence in the western population is 0.7 to 1.6 percent. [10]

The most common type is type 1vWD (75%) while the least common is type 3[2]. However, in the developing countries, type 3 seems to be commoner with higher association with positive family history and consanguinity. [3]

Amongst the inherited bleeding disorders, vWD is the most common and also the most difficult to diagnose. Clinical symptoms of vWD include predominantly mild mucosal bleeding; surgical bleeding may occur with specific challenges and joint bleeding can occur in the most severe forms. A family history either of diagnosed vWD or of bleeding symptoms is typically present. Laboratory diagnosis requires a series of assays of von Willebrand factor (vWF) quantity and function, and factor VIII activity, with no single straightforward diagnostic test available to either confirm or exclude the diagnosis. Newer assays of vWF function are becoming more available and useful in determining the laboratory diagnosis of vWD. [11]

A review done by Paula D. James and David Lillicrap, concluded that, most of type 2 variants and type 3 are relatively easy to diagnose but the diagnosis of type 1 vWD remains problematic. They have also found that the assessment of clinical bleeding phenotype with objective quantifiable scoring systems for mucocutaneous bleeding are helpful in identification of clinical bleeders and estimating the severity of the phenotype in adults and also in children and provide more objective measure of bleeding tendency that can be easily communicated between health care professionals. [9]

A cross sectional study done on already diagnosed patients with vWD in Pakistan in 2012-13, aimed to determine the clinical presentation and frequency of types of vWD, found that type 3 was the commonest (94.12%) type , a positive family history was found in 86.27% and consanguinity in 82.35%. This was attributed to the high prevalence of consanguineous marriages in their society. There had been not much difference among the proportions of males(50.98%) and females(49.02%). Easy bruising and epistaxis were the commonest presentations whereas menorrhagia was the commonest in females among childbearing age.[3]

When compared to world studies, there is a significant gap of knowledge about vWD in Sri Lanka asno analytical study has been performed up to now.

It is thought that vWD is under diagnosed because people with mild signs and symptoms may not seek medical attention. In Sri Lanka, patients with increased bleeding tendency are investigated by haematologists in local hospitals and sent to the reference laboratory, the Medical Research Institute (MRI) to exclude vWD, where further evaluation and specific laboratory investigations are done.

Therefore, we conducted this research to analyze clinical characteristics and laboratory investigations in patients with von Willebrand disease in Sri Lanka, and to assess the usefulness of BAT score as a screening tool in bleeder screening.

2. MATERIAL AND METHODS

This was a retrospective cross-sectional study, conducted at a tertiary reference centre (Medical Research Institute) in Sri Lanka. The study was done on 47 diagnosed patients with vWD, from 2012-2017at MRI, to analyze clinical and laboratory characteristics of them.

Data were taken from all the patients who were referred to bleeder screen from various parts of the country, in MRI hematology laboratory from 2012 – 2017. Among them, the 47 patients who were diagnosed as von Willebrand Disease, were selected anonymously as the study sample.

Data about clinical characteristics including clinical presentation, bleeding pattern and BAT (Bleeding Assessment Tool) score, family history, demographic data and the results of laboratory analysis were obtained using the clinical records available at Medical Research Institute (MRI)

Clinical assessment for bleeding has been done using the ISTH- BAT score based on clinical records and the laboratory data were collected from patient's records including full blood count (FBC), primary coagulation profile including Prothrombin Time(PT), Activated Partial Thromboplastin Time(APTT), Thrombin Time(TT), Fibrinogen and vWD diagnostic profile consisting of von Willebrand factor Antigen (VWF: Ag), von Willebrand factor activity (VWF:Rico) and factor VIII assay and Ristocetin Induced Platelet Aggregation (RIPA). Patients have undergone full blood count analysis and blood group antigen detection.

All the laboratory tests were done at MRI haematology laboratory. Coagulometer ACL ELITE pro was used for the basic coagulation profile. vWFAg and activity measurements were done using Immunoturbidometric method, Factor VIII assay was done by one-stage assay based on APTT/Coagulation based method, the RIPA was done by Helena Aggram light transmission platelet aggregometer with absent/reduced platelet agglutination with Ristocetin 1.2 mg/ml corrected by mixing with normal plasma and the Full Blood Count analyzer ,Sysmex pocH100i used to do the FBCs.

The BAT score data were obtained from the clinical records and the score assessment was done by directly interviewing each patient at the time of referral.

2.1 Laboratory definition of von Willebrand disease

FVIII, vWF:Ag and vWF activity were measured. vWF level and activity<0.3 IU/ml was taken as cut off level for the diagnosis. A function: antigen ratio of <0.6 was used to identify patients with type 2 VWD. RIPA was performed on all patients with reduced VWF:RCo/VWF:Ag ratio.[15]

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

3. RESULTS AND ANALYSIS

This study included 47 patients who were diagnosed with Von Willebrand disease. There were 12 (25.5%) males and 35 (74.5%) females with a male: female ratio of 0.34 : 1.

Age range was 2 to 58 years. Among them most (70%) of the cases were diagnosed in 2014-2016. Cases were detected from all the 9 provinces of the country and most (15,34.8%)were detected from the Western province, 20% were from the Northern province, and 9.3% each from Southern and Eastern provinces. (Table 1)

***Table 1**- Provincial detection of vWD patients with the percentage*

Province	Number (n= 43)	Percentage
Western	15	34.8
Northern	9	20.9
Eastern	4	9.3
Southern	4	9.3
Uva	3	6.9
Northwestern	3	6.9
Sabaragamuwa	2	4.6
Central	2	4.6
North- Eastern	1	2.3

In our study, the commonest type was type 1 (31, 70.2%), the second commonest was type 2B/Platelet type VWD (8, 17%) and type 3 (8, 17%). (Table 2)

***Table 2-** Types of the vWD with the percentage of patients found in each category*

Type of VWD	Number	percentage
Type 1	31	70.2
Type 2B/Platelet type	8	17
Type 3	8	17

The average BAT score for each type of VWD was calculated.

***Table 3-**BAT score for each type of vWD*

Type of VWD (n=46)	Average BAT score
Type 1	5.9
Type 2B	6.8
Type 3	8.6

Type 3 disease showed the highest average BAT score followed by type 2B disease which is compatible with their bleeding severity. However, we could not find a statistical significance in this(P =0.231) hence we can conclude that mean BAT score is the same for all types.

3.1 Type of bleeding

The majority had bleeding from oral cavity and minor wounds as the commonest presentation followed by bleeding from the oral cavity. None had CNS bleeding. Haemarthrosis, gastrointestinal and muscle bleeding were the rarest presentations. Menorrhagia and post-partum haemorrhages were seen in 32% and 14% respectively in females of child bearing age. (Table 4)

Table 4-*Bleeding manifestations in the patients with vWD*

Bleeding manifestation	**Number(n=43)**	**Percentage**
Epistaxis	9	20
Bleeding from oral cavity	30	70
Cutaneous bleeding	20	46
GI bleeding	5	11
Bleeding from minor wounds	27	62
Menorrhagia	14	32
Post-partum haemorrhage	6	14
Tooth extraction	16	32
Surgery	4	09
Haemorrhoids	1	02
CNS	0	0

Blood group was not done in 28 out of 47 patients in the study population. Among the 19 patients who had undergone blood group analysis, the commonest was blood group O (40.4%)

The mean haemoglobin was 11.5g/dl (SD 1.58) and the mean platelet count was 245.5 x 109/l (SD 116.9)

APTT was prolonged in 31(66%) and was normal in 16 (34%) .APTT with each type of vWD and average BAT score were compared. (Table 5)

Table 5- *Comparison of APTT with BAT score in each type of vWD*

Type of vWD	**Normal APTT**	**Prolonged APTT**	**Average BAT score**	**Total *(n=47)***
Type 1	12	19 (61%)	5.9	31
Type 2B	01	07(87.5%)	6.8	08
Type 3	03	05(62.5%)	8.6	08

BT was prolonged in 21(44.7%) and was normal in 26 (55.3%) patients
The study revealed, positive family history in 27 (57.4%), negative family history in 17 (36.2%) patients and family history was unknown in 3(6.4%) patients. 11(23.4%) patients were products of consanguineous marriages, whereas 32(68.1%) patients were from non-consanguineous marriages and 4 (8.5%) it was unknown.

Table 6(n=44)*- Presence of family history in each patient with vWD*

Type of VWD	Family history present	Family history absent
Type 1	20(69%)	9(31%)
Type 2B	1(12.5%)	7(87.5%)
Type 3	6(86%)	1(14%)

When each type of vWD considered Type 3 and Type 1 VWD showed higher association with a positive family history respectively.

4. DISCUSSION

The aims of this study were to analyze demographic, clinical and laboratory characteristics of patients diagnosed with vWD at the Medical Research Institute, Colombo, Sri Lanka, and to assess the usefulness of ISTH BAT score as a screening tool in bleeder screening in terms of, BAT score vs presence of vWD, BAT score vs type of vWD and to assess the significance of APTT value and presence of vWD in the study population.

There was female preponderance with a male to female ratio of 0.34:1. In some studies done in Pakistan, there was no such difference in the gender ratio [3]. The predominance in females could be due to more bleeding symptoms in them with menorrhagia and postpartum haemorrhages which prompted to investigate them further leading to detection and confirmation.

The commonest type was type 1(70.2%). Type 2B/Platelet type and type 3 were detected in equal numbers. (Table 2)

This is different from the prevalence pattern of some Asian countries where the commonest type is Type 3 vWD[3]. Among the 8 patients detected as type 2B, 5 were from north and east provinces, out of which 3 were from one kindred, a family identified at Akkareipaththu at Ampara District. This fact highlights the importance of screening, genetic counseling and health education needed in these targeted populations.
The prevalence pattern of subtypes of vWD of developed countries matches with ours. Several studies have been done on patients with von Willebrand Disease in many countries such as India, Pakistan, Italy, Argentina, Taiwan and Europe. From those research studies,vWD type 1 is identified as the commonest type in developed countries (ranging from 40% to 90% of all vWD cases), whereas type 3 predominates in developing countries such as India and Pakistan. The frequency of qualitative (i.e., type 2) vWD ranges from 3% to >50% of all vWD cases, as does the frequency of specific qualitative vWD types (i.e., 2A, 2B, 2M, and 2N). Although type 2A vWD is considered the most common form of type 2 vWD, some reports consider type 2M as commoner[3][8][10][12][18][19].Overall, the majority of patients are found to be type 1(75%). Types 2A and 2B appear to be common, together accounting for about 15%. Type 3 is the least frequent and has a prevalence of 1–2 in 106 globally. Although some forms remain difficult to classify according to the standard classification system and they may show features of more than one type [2].

Bleeding time was normal in 44.7% and prolonged in 55.3% of the sample. Though it is freely available in poor resource settings seen in our country, it is not helpful in screening or diagnosis.

APTT was prolonged in 66% of patients. Table 5 elaborates the relationship of average BAT score in each type with APTT. In Type 2B vWD, 7 out of 8 patients had prolonged APTT, but the average BAT score was less than the Type 3 vWD, in which 5 out of 3 patients got prolonged APTT.
The highest average BAT score was seen in type 3 vWD which is compatible with the bleeding severity of that category.
In our study, positive family history was seen in 27 (57.4%), negative family history in 17 (36.2%) patients and family history was unknown in 3(6.4%) patients. Type 3 and type 1 vWD patients showed higher association with a positive family history (Table 6).

Some studies conducted in Asian countries have revealed a higher prevalence of consanguineous marriages with a higher percentage of presence of positive family history [3]. However, the higher association with a positive family history in our study suggests the value of the family history is incorporated into BAT score especially in detecting type 3 and type 1vWD.

5. CONCLUSION

With our study, we conclude that in Sri Lanka, vonWillebrand disease Type 1 is higher compared to the other types. The value of basic bleeder screen such as bleeding time and APTT are limited due to its insensitivity. When screening for vonWillebrand disease, BAT score adds value to initial screening particularly when combined with family history.

CONSENT

Data about clinical characteristics including clinical presentation, bleeding pattern and BAT (Bleeding Assessment Tool) score, family history, demographic data and the results of laboratory analysis were obtained using the clinical records available at Medical Research Institute

ETHICAL APPROVAL

Obtained from the Ethical review committee of University of Sri Jayewadenapura, Sri Lanka.

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