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Frequency of Von Willebrand Disease and its Types: Data from a Tertiary Care Hospital of Karachi, Pakistan

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Abstract

Objective: The aim of the present study is to determine the frequency and types of von Willebrand disease in a tertiary care hospital of Karachi, Pakistan.

Methodology: This retrospective cross-sectional study was conducted in the section of haematology and transfusion medicine, Department of Pathology and Laboratory Medicine, Aga Khan University Hospital, Karachi, from May 2020 to April 2021 after the approval from Ethical Review Committee (2020-3537-10215). The consecutive blood samples of both genders and of all ages received within the study period for the diagnostic workup of vWD were included. The data was analysed using SPSS version 20.

Results: A total of 552 samples for VWF Ag were received. vWD was identified in 47(8.5%) of the samples, and 505 patients had no disease. Female to male ratio was 1.5:1. The median age was 11 years (ranges from 10 days to 70 years). Thirty (5.4%) of patients had Type I disease, 11 (2%) patients had type III, and out of 47 patients, 6 (1%) patients were diagnosed to have type II disease, while 19 (3.4%) patients had low VWF Ag due to other causes.

Conclusion: In the current study, type I vWD was found to be the most common type, whereas other studies from Pakistan have commonly reported type III.

Keywords: Von Willebrand, bleeding disorder, hemophilia , thromboplastin

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Introduction

Von Willebrand disease is the most common inherited bleeding disorder. It is classified into 3 main types, type I and III are quantitative defects, whereas type II is qualitative defect which is further sub-classified in to II-A, II-B, II-M, II-N. Von Willebrand factor (vWF) is a large, complex, multimeric plasma glycoprotein synthesized by vascular endothelial cells stored in the Weibel–Palade bodies prior to release and by the megakaryocytes. vWF has two important roles in haemostasis. Firstly, it acts as carrier protein for factor VIII (FVIII) preventing its proteolytic degradation in plasma and secondly, it acts as an adhesion protein between platelet and the endothelium helping in primary platelet plug formation.[1]

Von Willebrand disease (vWD) is an autosomal hereditary bleeding disorder, associated with a partial or complete, i.e. quantitative (Type I & III respectively) or qualitative (Type II) defect of vWF.[2] Patients with vWD present with spontaneous or traumatic mucocutaneous bleeding usually early in life depending on the severity of the disease. Women with vWD can present with menorrhagia and post-partum bleeding.

Although the data for the frequency of vWD in Pakistan is limited, some of the institutes have reported it as 3.18% to 7.74%.[3] Consanguinity plays an important role in the overall incidence and frequency of heritable bleeding disorders. In Pakistan, consanguineous marriages are practiced on a large scale and hence higher frequency of bleeding disorders.[4]

Based on the availability of specific diagnostic tests, laboratory testing of vWD vary in different centres.[5] In the presence of strong clinical history of bleeding, the vWD is diagnosed with the help of prolonged activated partial thromboplastin time (APTT) and bleeding time (BT), low levels of FVIII, vWF antigen and for qualitative type II, ristocetin induced platelet aggregation, ristocetin cofactor activity (Rcof), collagen binding assays and multimeric analysis of vWF protein are offered.[6]

Methodology

This cross-sectional study was conducted in the section of haematology and transfusion medicine, Department of

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Pathology and Laboratory Medicine, Aga Khan University hospital, Karachi, from May 2020 to April 2021.

The consecutive blood samples of both genders and of all ages received within the study period for the diagnostic workup of vWD were included. vWF antigen (vWFAg) was performed by immunoturbidimetric assay, and vWF activity was assessed through Rcof in a citrated plasma performed on Sysmex CS-2500 coagulation analyzer. FVIII was performed by clotting based assay on Sysmex CS-2500.

Patients were diagnosed as having type III, I, II and Low vWFAg if the vWFAg was less than 5%, between 6-30%, VWF: RCOF/VWF:Ag ratio of less than 0.6 and VWFAg was between 30-50% respectively. Patients' demographics, including age, gender, APTT, BT, FVIII level, vWFAg, and Rcof, extracted through integrated laboratory management system. The data was analysed using SPSS version 20. Mean ±SD was used for quantitative variables while frequencies and percentages were used for categorical variables.

Results

A total of 552 samples for VWF Ag were received. vWD was diagnosed in 47(8.5%) of the samples and 505 patients had no disease as shown in figure 1. Female to male ratio was 1.5:1(shown in figure 2). Median age was 11 years (ranges from 10 days to 70 years). Thirty (5.4%) of patients had Type I disease, 11 (2%) patients had type III, and out of 47 only 6(1%) patients were diagnosed to have type II disease while 19(3.4%) patients had low VWF Ag.

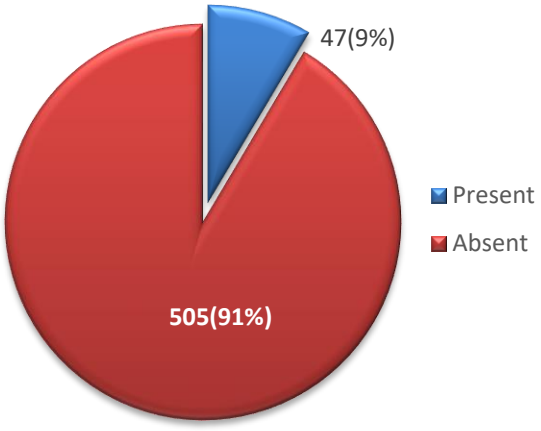

Figure 1. Distribution of VWD in samples received for testing

Out of 552 patients, only 42 requested bleeding time tests, which showed mean bleeding time of 3.09 minutes. The range of bleeding time included 1-8 minutes and only one patient had bleeding time of more than 7 minutes, whereas rest 41 results were in normal range.

Out of 552 patients, 108 patients had available haemoglobin levels, ranging from 1.3 to 16 gm/dl with mean haemoglobin of 10gm/dl.

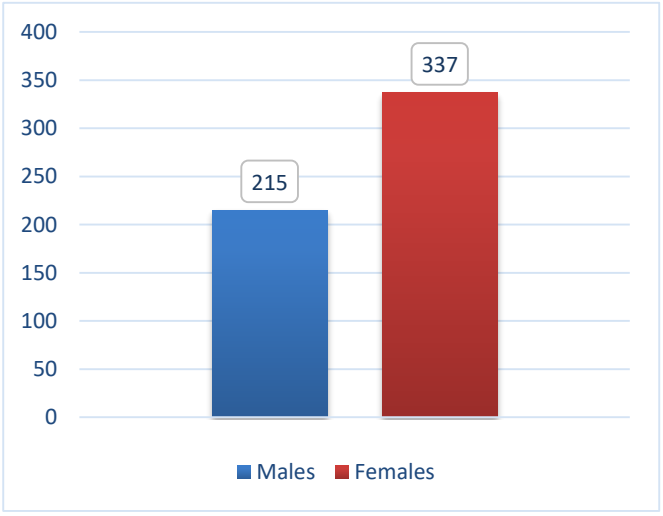

Figure 2. Gender distribution of samples received for VWF testing

Discussion

vWD is the most common inherited bleeding disorder. The disease is categorized into either qualitative defect or quantitative defect in vWF. Quantitative defect includes type I and type III i.e. partial, and complete deficiency of VWF respectively. Type II is the qualitative defect of vWF, further sub-classified into II-A, II-B, II-M, II-N. Individuals with vWF Ag between 30-50% are labelled as "low vWF''.

The identification of type of vWD is important for certain purposes like pattern of inheritance, patient counselling, to differentiate type III from haemophilia A and for prophylactic and management purpose e.g.: desmopressin is not given in Type II-b vWD and Type III vWD.[7]

Bleeding score together with family history and a baseline screening workup, help in the diagnosis of vWD. Screening tests for vWD include a full blood count,

bleeding time, PFA-100, prothrombin time, activated partial thromboplastin time. The specialized test includes vWFAg, vWF activity by ristocetin cofactor binding assay and/ or collagen binding assay, FVIII levels, RIPA, and multimer analysis. However, molecular studies are confirmatory[8]. A new assay i.e. vWF:GPIbR which uses recombinant GPIbα fragments tethered to microparticles, and eliminate the use of whole platelet, the test is more sensitive than vWF:RCo and is available in Canada and Europe.[9]

Our institute has a reference laboratory that receive samples for specialized testing from all over the country. We perform vWFAg and Rcof binding assay under strict internal quality control and participate in external quality assurance programmes. However, currently von Willebrand multimer analysis, collagen binding assay and RIPA are not available in our institute.

We analysed 552 samples requested for vWFAg, the frequency of vWD in our study was found to be 8.9% which was found to be close to the one reported by Kaleem *et al.,* in 2014 i.e., 10%[10]. In 2010 Sandip *et al.,* study conducted in India showed same 10% frequency of vWD[11] while PK Gupta *et al.,* study of India conducted in 2005 showed vWD frequency of 16.8%.[12]

Comparatively there was a slight difference in frequency of types of vWD. In our study type I came out to be most common, which was 5.6% (out of 8.9%) whereas in other studies type III was most common, Borhany *et al.,* reported type III to be (51.4%) most common[13], in Sucheta *et al.,* study type 3 was 59.5%[14]. Kaleem *et al.,* also reported type-3 the most common type.[10] Similar results to our study were found in Sandip *et al.,* which identified type I to be most common 42.5%[11], Veronica *et al.,* in 2018 also reported type I as 84.5%.[15]

We compared the most frequent types of the disease according to age groups, i.e., 51 patients with vWD were up to 18 years of age and out of them 23 (45%) had type I disease. The other age group included 19 to 50 years in which 14 diseased patients were included, and 7(50%) had type I disease. The third age group was above 50 years in which only 1 had type II vWD disease.

The low plasma vWFAg is divided into another entity, patients with markedly reduced plasma vWF levels are categorised into type I vWD and they present with bleeding phenotypes, whereas other entity includes moderately low vWFAg i.e. between 30-50 IU/dL and they are identified as low vWF levels, such patients present with variable bleeding phenotype and they do not have vWF gene sequence variations and they are not classified as a disease.[16] The variability of vWF levels make diagnosis of low vWF complex, which basically depends on multiple factors which can be environmental or genetic, including physical activity, certain infections, increasing age and pregnancy state whereas the clinical presentation of such a population with low vWF is non-specific and there is no significant difference of bleeding diathesis between healthy population and patients with low vWF.[17]

There were certain limitations in our study; the clinical details of patients were not available, so we could not assess the severity or inheritance of the disease. For samples which were received for vWFAg, not all had requested vWF: Rcof activity in our laboratory. In addition, vWF: collagen binding assay, RIPA and VWF multimer analysis was not available in our laboratory. Therefore, due to lack to availability of data and test methods classification of type I and II may have been underdiagnosed.

Conclusion

We concluded that the frequency of vWD in our hospital was 8.5%. Despite certain limitations in our study, e.g., unavailability of data regarding bleeding history, and limited test assays availability, type I as the most common in our study, whereas type III has been commonly reported in national literature.

References

1. Sadler JE. Biochemistry and genetics of von Willebrand factor. Annual review of biochemistry. 1998;67:395.
2. Sadler JE, Budde U, Eikenboom JC, Favaloro EJ, Hill FG, Holmberg L, Ingerslev J, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J. Thromb. Haemost. 2006 Oct;4(10):2103-14.
3. Saeedi MI, Raziq F, ur Rehman M, Ahmad H. Von Willebrand disease. J. Postgrad. Med. Inst. 2001;15(2).
4. Hussain R. Community perceptions of reasons for preference for consanguineous marriages in Pakistan. J. Biosoc. Sci. 1999 Oct;31(4):449-61.
5. Adil SN, Qureshi MA. Von Willebrand disease-an under diagnosed entity. J Pak Med Assoc. 2008 Apr 1;58(4):157.

6. Echahdi H, El Hasbaoui B, El Khorassani M, Agadr A, Khattab M. Von Willebrand's disease: case report and review of literature. Pan African Medical Journal. 2017 Aug 8;27(1).
7. Castaman G, Goodeve A, Eikenboom J. Principles of care for the diagnosis and treatment of von Willebrand disease. Haematologica. 2013 May;98(5):667
8. Roberts JC, Flood VH. Laboratory diagnosis of v on W illebrand disease. Int. J. Lab. Hematol. 2015 May;37:11-7.
9. Bodó I, Eikenboom J, Montgomery R, Patzke J, Schneppenheim R, Di Paola J; von Willebrand factor Subcommittee of the Standardization and Scientific Committee of the International Society for Thrombosis and Haemostasis. Platelet-dependent von Willebrand factor activity. Nomenclature and methodology: communication from the SSC of the ISTH. J Thromb Haemost. 2015;13(7):1345-1350.
10. Khan MK, Khan SQ, Malik NA. Spectrum of Von Willebrand's disease in Punjab: clinical features and types. Journal of Ayub Medical College Abbottabad. 2014 Dec 1;26(4):470-3.
11. Kumar S, Kishore R, Gupta V, Jain M, Shukla J. Prevalence and spectrum of von Willebrand disease in Eastern Uttar Pradesh. Indian J. pathol. microbiol. 2010 Jul 1;53(3):486.
12. Gupta PK, Charan VD, Saxena R. Spectrum of Von Willebrand disease and inherited platelet function disorders amongst Indian bleeders. Annals of hematology. 2007 Jun;86(6):403-7.
13. Borhany M, Shamsi T, Naz A, Farzana T, Ansari S, Nadeem M, Rehman ZU, et al. Clinical features and types of von Willebrand disease in Karachi. Clin. Appl. Thromb./Hemost. 2011 Nov;17(6):E102-5.
14. Trasi S, Shetty S, Ghosh K, Mohanty D. Prevalence & spectrum of von Willebrand disease from western India. Indian J Med Res. 2005 May 1;121(5):653.
15. Flood VH, Abshire TC, Christopherson PA, Friedman KD, Gill JC, Montgomery RR, Haberichter SL, Zimmerman Program Investigators. Von Willebrand disease in the United States: perspective from the Zimmerman program. Annals of blood. 2018 Jan;3.
16. Lavin M, O'Donnell JS. How I treat low von Willebrand factor levels. Blood, The Journal of the Am Soc Hematol. 2019 Feb 21;133(8):795-804.
17. Nichols WL, Hultin MB, James AH, Manco-Johnson MJ, Montgomery RR, Ortel TL, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA) 1. Haemophilia. 2008 Mar;14(2):171-232.