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Epidemiological, Demographic, and Clinical Characteristics of Von Willebrand Disease Patients in Zahedan City, Iran: A Descriptive Study

Majid Naderi[1], Benyamin Rhmati[2], Hoora Ganjali[3], Saeedeh Yaghoubi[4], Mohammad Sadra Harifi-Mood[5], Seyed Ghader Azizi[5]

[1]Genetics of Non-Communicable Disease Research Center, Zahedan University of Medical Sciences, Zahedan, Iran
[2]Blood Transfusion Research Center, High Institute for Research & Education in Transfusion Medicine, Tehran, Iran
[3]Faculty of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran
[4]Department of pediatrics, Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran
[5]Clinical Immunology Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

Corresponding Author: Seyed Ghader Azizi, Clinical Immunology Research Center, Zahedan University of Medical Sciences, Zahedan, Iran
E-mail: s.ghaderazizi@yahoo.com

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ABSTRACT

Background: Von Willebrand disease (VWD) is one of the most common coagulative diseases, so identifying the effective factors in preventing this complication is essential. The study aimed to evaluate the frequency of demographic and epidemiological findings in VWD patients referred to a hospital in Zahedan, Iran.

Materials and Methods: This study was performed on 76 patients with VWD referred to Hazrat Ali-Asghar Hospital in Zahedan City, Sistan, and Baluchestan province. After obtaining consent from the patients, the demographic information and clinical symptoms of the disease were recorded. All statistical analyses were performed using SPSS 22.0 software. All descriptive data were expressed as mean ±SD and percent (%) depending on the continuous and dichotomous variables. A P-value ≤0.05 was considered significant statistically.

Results: The present study results showed that the highest age group of VWD patients at the time of disease diagnosis was in the age group 1-5 years (47.3%), and most patients had type III VWD (80.3%). It was also found that 67.1% of patients had a positive family history and their parents' consanguineous marriage (77.6%). The most common complaints were epistaxis (88.15%), cutaneous bleeding (78.94%), and oral cavity bleeding (61.84%), respectively.

Conclusion: Due to the high prevalence of VWD in consanguineous marriages and an increase in adverse complications and symptoms in VWD patients, proper diagnosis and screening at an early age, especially in people with family history, is essential. Efforts are needed to develop national registries and widely provide the required and available basic services for diagnosis and treatment.

Keywords: Von willebrand disease; Demographics; Epidemiologic; Clinical

INTRODUCTION

As a sizeable multimeric glycoprotein in plasma, the von Willebrand factor (VWF) contributes to platelet adhesion at the bleeding site and plays critical role in initiating homeostasis [1,2]. Two critical roles of VWF have been reported in homeostasis: platelet adhesion to the vessel endothelium during vascular injury; and as a specific vector for coagulation factor 8[3]. The Von Willebrand disease (VWD) term encompasses the widespread primary (decrease in

plasma levels of VWF) or secondary (defect in VWF function) deficiencies in VWF[4]. In addition to endothelial cells, the platelets also contain VWF storage produced by platelet precursors, e.g., megakaryocytes[3]. The prevalence of VWD is generally estimated between 1/100 and 1/1000 individuals according to abnormal bleeding symptoms [5].

Two forms of this disease have been introduced: acquired and inherited forms. Inherited forms are divided into three main types [6]; approximately 70% of all cases are in type 1 (mild type) VWD, which is inherited autosomally and characterized by a reduction in factor 8 level, VWF blood level with correct function, and ristocetin cofactor (VWF:RCo) activity. The VWF:RCo is a test for evaluating VWF activity and platelet agglutination in the presence of ristocetin [7, 8]. Patients with type 1 VWD usually have mild to moderate bleeding during surgery/dental procedures [7]. Type 2 VWD is a qualitative deficiency with predominantly or recessively heterozygous mutations of dysfunctional VWF in 20-30% of patients, in which the VWF level is normal. severe clinical manifestations than type 1 [9, 10]. The last type is type 3 (severe type), which has severe manifestations with heavy bleeding similar to hemophilia. This type results from the inheritance of two abnormal VWF alleles, which affects up to 5% of all cases. These patients have very low or no VWF and VWF:Rco activity[10, 11]. In other words, types 1 and 3 are quantitative defects, but type 2 is a qualitative defect of VWF in this disorder [6 ،8].

Complete blood cell counts (CBCs) and other blood tests may be normal in early laboratory evaluations; however, microcytic anemia or thrombocytopenia are more common. The kind of disease could then be determined by measuring the level and function of VWF, PT (prothrombin time), PTT (partial thromboplastin time), BT (bleeding time), CT (clotting time), and factor 8 levels [4, 12].

The typical clinical coagulation signs in these patients are prolonged mucosal cutaneous bleeding from the nose (epistaxis) and mouth, usually after small incisions and surgery; childbirth in women; bruises without trauma history; menorrhagia, especially in women with a genetic background; joint bleeding (hemarthrosis), and gastrointestinal bleeding [13-15].

In developing countries, there is insufficient knowledge about VWD. A 1998 survey found that less than one-third of VWD patients had been identified globally. Particularly in nations with a high proportion of consanguineous marriages, the severe type of VWD was more common (up to 50%) among those groups[16]. The number of detected patients was less than 20% of the projected number among the eight Asian countries (India, Malaysia, Iran, Oman, Nepal, Thailand, Singapore, and Saudi Arabia). It has been claimed that VWD is not very common in Iran. Accordingly, only 6.5% of patients with coagulation problems (367 cases) had VWD, with 50% of cases having been documented in the severe form[16,17]. Whether this data represents a real difference in VWD prevalence or is related to the fact that VWD diagnosis could be difficult and may have been overlooked, especially in mild cases, is unknown.

In general, there is limited information about VWD in Iran, and no information about this disease is available in Sistan and Baluchestan province. However, due to the high prevalence of consanguineous marriage in Sistan and Baluchestan province, which is known as the most important cause of type 3 VWD (the most severe type of this disease)[14], this study aimed to evaluate the frequency of demographic and epidemiological findings in VWD patients referred to Ali-Asghar Hospital in Zahedan city, the capital city of Sistan and Baluchestan province, Iran.

MATERIALS AND METHODS

Study population

This cross-sectional study included 76 patients with a confirmed diagnosis of VWD, ranging in age from eight months to 45 years, who were sent to Ali-Asghar Hospital in Zahedan city, Sistan, and Baluchestan province, between April 1, 2017, and March 30, 2018. Written consent that had been obtained had been signed by each patient. The patients observed no problems that went against medical ethics, and efforts were taken to protect the patients' medical information because this study lacked unique interventions and solely examined the patients' medical records.

Patient characteristics and data collection

Required baseline characteristics of patients included sex, age at diagnosis, clinical signs at the time of referral and after treatment (such as epistaxis, easy bruising, bleeding, and menorrhagia in women), VWD family history, VWD type (1, 2, or 3 types), consanguineous marriage, and complications of the disease (such as anemia, hepatitis B, hepatitis C, and arthropathy), which were collected through reviewing the medical records of patients or interviews with the patient and then collected in questionnaire form. In cases of defects in medical records and no VWD, patients were excluded from the study.

Statistical analysis

All statistical analyses were performed using SPSS software version 22.0 (Chicago, IL, USA). Descriptive analysis of data was represented in mean±SD, or median, and percent (%). Continuous variables were expressed as mean±SD or median. Dichotomous variables were expressed as a percent (%). A P-value ≤0.05 was considered significant statistically.

RESULTS

The demographic and clinical characteristics of patients are shown in Table 1 and Table 2. A total of 76 patients with VWD diagnoses were included in this study. Thirty-seven patients in our study (48.7%) were males (P<0.0001), and 39 patients (51.3%) were females. At the time of diagnosis, the mean age was 14.33±8.68 years (8 months-44 years). According to the results, the highest age group of people with VWD at the time of disease diagnosis includes less than one year (35.5%), 1-5 years (47.3%), 6-12 years (9.21%), 13-25 years (5.26%), and 25 years and more (2.63%), respectively.

It was also found that most of the patients had type III (80.3%), and other patients were categorized as type I (15.8%) and type II (3.9%). Fifty-one cases (67.3%) had a positive family history of the disease, and 59 cases (77.6%) had parents with consanguineous marriages. The most common complaints of patients include epistaxis in 68 cases (88.15%), cutaneous bleeding in 60 cases (78.94%), oral cavity bleeding in 47 (61.84%), minor wounds in 25 cases (32.89%), muscle and joint bleeding in 17 cases (22.34%), bleeding during dental surgery in 16 cases (21.05%), hematuria in 15 cases (19.73%), gastrointestinal bleeding in 14 cases (18.42%), menorrhagia in 13 cases (17.1%), after surgery bleeding in 7 cases (9.21%), and postpartum hemorrhage in 1 case (1.31%).

Table 1: Patient demographics and clinical characteristics (n=76)

Age at the diagnosis time	
Mean ± SD	14.33 ± 8.68
Range	8 months - 44 years
Sex, n (%)	
Male	37(48.7%)
Female	39(51.3%)
Type of vWD, n(%)	
Type 1	12(15.78%)
Type 2	3(3.94%)
Type 3	61(80.3%)
Family history of vWD, n(%)	
Yes	51(67.1%)
No	25(32.9%)
Consanguineous marriage, n(%)	
Yes	59(77.6%)
No	17(22.3%)
vWD clinical signs, n(%)	
Epistaxis	68(88.15%)
Cutaneous bleeding	60(78.94%)
Minor wounds	25(32.89%)
Hematuria	15(19.73%)
Gastrointestinal bleeding	14(18.42%)
Oral cavity bleeding	47(61.84%)
Bleeding during dental surgery	16(21.05%)
Bleeding after surgery	7(9.21%)
Menorrhagia	13(17.10%)
Postpartum hemorrhage	1(1.31%)
Muscle and joint bleeding	17(22.34%)

Table 2: Distribution of symptoms and complications among patients with vWD referred to Hazrat Ali-Asghar Hospital

Clinical signs	Type 1 of vWD,n(%)	Type 2 of vWD,n(%)	Type 3 of vWD,n(%)
Epistaxis	9(11.8%)	3(3.9%)	56(73.6%)
Cutaneous bleeding	9(11.8%)	2(2.6%)	49(64.4%)
Minor wounds	5(6.5%)	1(1.3%)	19(25%)
Hematuria	2(2.6%)	1(1.3%)	12(15.7%)
Gastrointestinal bleeding	3(3.9%)	2(2.6%)	9(11.8%)
Oral cavity bleeding	7(9.2%)	2(2.6%)	38(50%)
Bleeding during dental surgery	2(2.6%)	1(1.3%)	13(17.1%)
Bleeding after surgery	3(3.9%)	2(2.6%)	2(2.6%)
Menorrhagia	1(1.3%)	1(1.3%)	11(14.4%)
Postpartum hemorrhage	0(0%)	0(0%)	1(1.3%)
Muscle and joint bleeding	1(1.3%)	2(2.6%)	14(18.4%)

DISCUSSION

The prevalence of demographic and epidemiological traits in VWD patients sent to Hazrat Ali-Asghar Hospital has been assessed, as was previously indicated. The majority of VWD cases, or 47.3%, occurred within the first five years. 39 instances (51.3%) involved women, and 61 patients (80.3%) had VWD type III. 59 patients (77.6%) were consanguineous, and 51 patients (67.1%) had a family history of VWD.

Hussain et al. (2016) assessed the congenital deficiency of VWF in 778 patients with a bleeding tendency. In this study, VWD was diagnosed in 107 patients between 1 and 10 years old at the time of diagnosis, and a range of characteristics, including family history, clinical symptoms, and laboratory tests, were determined. The most common symptoms at the time of diagnosis were epistaxis (39.2%), gum bleeding (24.2%), and menorrhagia in female patients (23.4%). Family history was positive in all patients. Hepatitis C was rare in patients after the use of cryoprecipitate. Overall, the findings of this study showed that VWD is a common inherited hemorrhagic disease in Iraq, most often manifested as minor bleeding involving the mucocutaneous, and mainly in early childhood and children with a positive history [18]. With the exception of our study's smaller disparities in demographic parameters, the prevalence of symptoms was similar to our findings.

In Khan et al. study in Pakistan [14], it has been studied the clinical features and types of VWD on 51 patients with VWD. Patients were diagnosed based on prolonged BT, abnormal APTT, and decreased levels of VWF, FVIII, VWF: RCo, and VWF: RCo/VWF ratio. Among 51 patients, 26 cases (50.98%) were male, and 25 cases (49.02%) were female. Type 3 of VWD (94.12%) was recognized as the most common type. Easy bruising was the most common clinical manifestation observed in 21 patients (41.18%), followed by epistaxis (13.73%), gum bleeding (7.84%), menorrhagia (9.80%), hemarthrosis (3.92%), hematoma formation (9.8%), bleeding after circumcision (3.92%), and bleeding after surgery (3.92%). Consanguineous marriage was reported in 42 (82.4%) patients, and a family history of bleeding disorders was also reported in 44 (86.27%) cases. Overall, this study showed that type 3 VWD was the most common type of disease, and mild bruising and epistaxis were the most common clinical manifestations. These findings are consistent with ours, except for the higher prevalence of type 2 in Khan's study.

The frequency of VWD, its types, and clinical features of the disease among women with menorrhagia in Kermanshah province were evaluated by Payandeh et al. After excluding patients with confounding factors among the 482 participants, 56 patients were evaluated for hereditary bleeding disorders. VWD was identified in 31 patients. VWD type 3 was the most dominant subspecies[19]. The study's findings regarding the prevalence of different types of VWD are in line with the findings of our study. In our study, it was found that most of the patients had type 3 (80.3%) and then type 1 (15.8%) and type 2 (3.9%), but in this study, type 2 (32.3%) was the most common after type 3 (45.2%).

Mohsin S. et al. in Pakistan investigated the clinical symptoms and consequences of VWD. Out of 426 individuals from the Lahore Hemophilia Association, 57 were diagnosed with VWD based on clinical features, extended BT and PTT, and decreased VWF antigen testing. The majority of patients (49.1%) were diagnosed within a year, followed by 35% between the ages of 1–5 years and 15.8% after more than five years. In 60% of the patients, there was a family history of bleeding disorders. Epistaxis, bruising, and menorrhagia were the most common clinical signs of the condition. Problems of the disease were reported in 35% of patients, with hepatitis C being the most prevalent (31.6%), followed by arthropathy, CNS problems, and hepatitis B, which were observed in 22.8%, 1.8%, and 1.8% of patients, respectively [15]. The findings were consistent with those from our investigation. Furthermore, it was discovered that the majority of cases with VWD at the diagnosis were young (less than five years), according to our results.

In a study by Borhany M., the clinical features and types of VWD have also been investigated in patients with a positive history of congenital bleeding disorders or a tendency to bleeding in Karachi province, Pakistan. Laboratory analysis revealed VWD in 68 cases (21.3%) of 318 participants, with a male-to-female ratio of 0.1:38 (31 vs. 37) and a mean

age of 17 years. Type 3 was the most common type, with a frequency of 35 cases (51.4%), followed by Type 2 with a frequency of 20 cases (29.4%), and finally Type 1 with a frequency of 13 cases (19.1%), similar to our study. Among all patients, the most common symptom was mucocutaneous bleeding in 55.8% of patients and menorrhagia among female patients. VWD, with a frequency of 21.3%, was the second most common bleeding disorder and the most common coagulation defect among women with menorrhagia[20]. However, in our study, the prevalence was higher in women than men, and nose and cutaneous bleeding were the most common manifestations of the disease.

CONCLUSION

According to our findings, the most common age group for people with VWD at the time of diagnosis was 1–5 years old, and the majority of the patients had type III, as well as a positive family history and consanguineous marriage between their parents. Patients' most prevalent complaints were epistaxis, cutaneous bleeding, and bleeding from the oral cavity. In conclusion, due to the high frequency of this disease in consanguineous marriages and the fact that VWD increases the risk of severe sequelae in patients, thorough diagnosis and screening at an early age, particularly in persons with a family history, as well as adequate treatment in old age, are critical. More efforts are needed to build national registries that provide at least basic services for patient diagnosis and treatment.

CONFLICT OF INTERESTS

The authors report no conflict of interest.

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