



Original article

Hemostatic profile detailing in apparent VWD cases: A cross sectional study



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ABSTRACT

The von willebrand disease (vWD) accounts to be one of the most common hereditary bleeding ailment that amounts its incidence to almost 1.5% of normal population. It is mostly associated with a defect in primary hemostasis as well as secondary defect in coagulation factor VIII as diagnosis of vwd happened to be challenging with earlier diagnostic criteria's. Testing Vwd in menorrhagia patients was not at ease. A cross-sectional study was conducted in female patients who have visited obstetrics and gynecology clinic at King Saud University Medical City (KSUMC), Riyadh, Saudi Arabia. The inclusion criteria consist of adult female patients between 16 and 45 years old with menorrhagia. A sample of 45 patients were screened and selected for the above-mentioned study. The SPSS Statistical analysis package was performed to analyze the data's. The fisher's exact test was conducted to compare the demographic variables. The independent samples *t*-test was conducted to compare the means of subjects. The P value of ≤ 0.05 considered as statistically significant. The cases manifested with a history of bleeding during periods stretching from 7 to 90 days. The vWD was reported in 6.6 % (n = 3) women out of the total 45 patients. The vWF: Ac mean \pm SD (51.4 \pm 6.3) and vWF: Ag Mean \pm SD (93 \pm 67) were significantly lesser in vWD patients with that of non-vWD (98.7 \pm 22.6) vs (116 \pm 42.4) (p = 0.027) (p = 0.032) respectively. WBC, ESR, MCV, MCH, Hemoglobin, PLT count, INR, PT, APTT and FVIII showed no significant difference among the groups (p > 0.05).

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1. Introduction

Von Willebrand disease (vWD) is the most common hereditary hemostasis condition, with a variety of different subtypes (Swami and Kaur, 2017). VWD is difficult to diagnose since it necessitates 1) a personal history of bleeding symptoms, 2) a family history of bleeding or VWD, and 3) confirmatory laboratory testing (Sharma and Haberichter, 2019). Von Willebrand disease (VWD) is treated

by correcting both the primary hemostasis defect caused by an inherited deficiency of von Willebrand factor (VWF) and the secondary defect of factor VIII coagulant function (FVIII:C) caused by the loss of VWF-mediated binding and stabilisation of this intrinsic coagulation factor in flowing blood (Mannucci, 2019). Von Willebrand factor (VWF), a blood glycoprotein, is involved in hemostasis and thrombosis. High molecular weight (HMW) multimers have a key role in platelet aggregation among VWF multimers. As a result, their absence causes von Willebrand disease (VWD) type 2A, a hemostatic illness (Horiuchi et al., 2019). VWD is divided into six types (1, 2A, 2B, 2 M, 2 N, and 3) based on genotypic, clinical, and laboratory phenotypic differences (Gill et al., 2015). VWF deficiency causes mucosal bleeding in the oropharyngeal, gastrointestinal, and genitourinary tracts, and menorrhagia is the most common symptom in women, with 80 percent or more experiencing it (Ragni et al., 2016). Mucocutaneous and soft tissue bleeding are the most common clinical manifestations, and the severity of

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bleeding symptoms varies depending on the degree of VWF and FVIII reduction, as well as other factors (Castaman and James, 2019). The fact that VWF deficiency and/or abnormality causes von Willebrand disease (VWD), the most common hereditary bleeding disorder, demonstrates the significance of VWF in haemostasis (Randi et al., 2018). Since vWF serves as the carrier protein for FVIII, a heterogeneous quantitative or qualitative deficiency in the von Willebrand factor (vWF) may be associated with a concurrent decrease in factor VIII levels (FVIII) (Echahdi, 2017). Excessive mucocutaneous bleeding, such as easy bruising, epistaxis, oral cavity bleeding, severe menstrual bleeding, gastrointestinal bleeding, and abnormal bleeding after dental work, delivery, and surgery, can occur in patients with VWD (Kalot et al., 2020). Initial testing for potential VWD involves looking at the patient's and family's bleeding symptoms, which usually include epistaxis, quick bruising, and other hemorrhagic symptoms (Goodeve, 2016). A bleeding condition occurs when there is a problem with hemostasis, or when clotting hampered (de Faria et al., 2016). The most common clinical symptom is epistaxis, which followed by hemarthrosis in men and menorrhagia in women. We were able to show that various bleeding manifestations were frequently linked with type 3 patients by comparing the incidence of bleeding symptoms in patients with type 3 and type 1 VWD (Tosetto et al., 2020). VWD is linked to a wide range of mutations or deletions in the VWF gene (Leebeek and Atiq, 2019). Patients with substantial decreases in plasma VWF levels (30 IU/dL) have significant bleeding phenotypes and should be called "type 1 VWD (Lavin et al., 2018).

Menorrhagia is found to be the one of the most common gynecological disorders in women and no underlying organic pathology is found in more than 50% of cases (Hassan et al., 2012). In adolescent populations, the occurrence of menorrhagia a bleeding disorder prevails up to 14–48% and the and these menorrhagic symptoms commonly attributed to von Willebrand disease (VWD), coagulation factor defects and platelet function anomalies (Hossain, 2010). The incidence of vWD in menorrhagia patients were accountable to almost 5 to 20%, whereas the incidence was as meagre as 1% in non-menorrhagic cases. FVIII and FX appeared to be higher in women with vWD during follicular phase than that of the non-vWD cases. The studies are explicitly acknowledged obstetric and gynecologic morbidity in females with von Willebrand disease (VWD) and menorrhagia proves to be a significant cause of iron-deficiency anemia and consequent morbidity (Kouides, 2005). A high prevalence i.e. 13–17% of von Willebrand disease (VWD) amongst women with menorrhagia in most of the studies (Friberg et al., 2006). Von Willebrand diseases is categorized into three sub types; the type 1 which holds for 70–80% of all VWD cases, type 2 holds for 20%, and type 3 for almost 5–10% of the cases occurring secondary as a resultant of absence of FVIII (Borhany et al., 2011). Vwd manifested as mild bleeding disorders (MBD) coupled with platelet function defects (PFDs) in more than 50% of the studies (MacEachern et al., 2015). Inherited bleeding disorders of mild severity are rather frequent in the general population. Von Willebrand disease is an example of how difficult it is to diagnose minor bleeding diseases (VWD) (Boender et al., 2016). The reduced von Willebrand factor (VWF) levels is a common backing factor in 20% of cases in women with Heavy menstrual bleeding (HMB) (Lavin et al., 2018). Menorrhagia happens at regular intermissions such as every 24–35 days but with disproportionate duration of more than seven days (Sweet et al., 2012). It is a common disorder of hemostasis instigated by qualitative or quantitative flaws in von Willebrand factor (vWF) (Miller et al., 2001). The main aim of the study is to detect vWD in Saudi population who have visited OB-Gyne clinic of King Saud University Medical City (KSUMC) using their hemostasis profiles.

2. Materials and methods

A cross-sectional study was conducted at King Saud University Medical City (KSUMC), Riyadh, and Saudi Arabia. A sample of 45 patients who had treated to the OB-Gyne clinic of KSUMC were screened for the study. The inclusion criteria consist of adult female patients between 16 and 45 years old with menorrhagia. The Pregnant women, patients with SLE, patients who are on oral contraceptive pills, patients with Rheumatoid arthritis, patients who are under hormonal therapy, patients who are diagnosed with malignancy undergoing treatment and patients who are diagnosed with premenopausal syndrome were excluded from this study.

The patients were advised to visit the Hematology clinic for follow-up on day 1, day 7 and day 22 of the cycle for the assessment of menorrhagia. On day 1 of the cycle, blood extraction and analysis for complete blood count, C-reactive protein, ESR, Coagulation screening test (INR, PT, aPTT), Bleeding time & Clotting time, Hormonal status, Factor VIII assay, and Von Willebrand Factor assay was performed to assess the menstrual cycle of each patient.

The SPSS Statistical analysis package version 21 was performed to analyze the data. The fisher's exact test was conducted to compare the demographic variables. To compare the means of subjects, the independent samples *t*-test conducted. The P value of ≤ 0.05 considered as statistically significant.

3. Results

The classically triggered partial thromboplastin time (aPTT), platelet count, and closure time are all screening assays (PFA-100 analyzer). The measurement of FVIII activity (FVIII: C), VWF antigen (VWF: Ag), and VWF ristocetin cofactor activity (VWF: RCo) allows the estimation of ratios (VWF: RCo/VWF: Ag and FVIII: C/VWF: Ag). Second-level-specific VWF assays are important for diagnosing VWF deficiency. The bleeding propensity in VWD is mainly caused by an inherited deficiency or malfunction of the multimeric glycoprotein VWF, which results in irregular platelet-vessel wall interactions and improper platelet plug formation (primary hemostasis). Initial laboratory tests for type 2A and type 2B VWD may be identical to those for standard or reduced VWF: VWF-platelet binding activity was significantly reduced at high Ag levels. VWF protein is undetectable in type 3 VWD and FVIII levels were reduced significantly. VWF: Ag levels are poor in type 1 VWD, and VWF-platelet binding activity is reduced. The level of FVIII reduced because of lower VWF levels, and the structure of VWF multimers should be essentially normal, with no noticeable decrease in large VWF multimers. Women with VWD should not begin pregnancy until their form, subtype, and treatments have been determined. Women with VWD who have VWF and FVIII basal levels >30 U/dL usually see their levels return to normal by the end of pregnancy and anti-hemorrhagic prophylaxis is rarely required. In form 1 VWD, pregnant women with FVIII: C and/or VWF levels less than 30 U/dL at the time of delivery must receive desmopressin after umbilical clamping and for the next 3–4 days.

The sample of forty-five patients coming under the age group ranging from 16 to 45 years who visited the gynecology clinic participated in the study. According to the table 1, the vWD was reported in 6.6 % (n = 3) women out of the total 45 patients. The mean \pm SD age of the patients reported with non-vWD is 41 ± 12 compared to vWD patients 41 ± 16). They manifested bleeding history during the periods stretching from 7 to 90 days. Among the non-vWD patients 11 patients, (24.4%) reported with diabetes and 7 patients (15.6%) were reported with hypertension. The anemia reported in 31 non-vWD patients (68.9%) while 3 patients (6.7 %) of them found to be VWD patients. The statistical Independent samples *t*-test was performed to analyze the laboratory results

Table 1
The clinical and demographic characteristics of patients.

	Non-vWD Patients (n = 42)		vWD Patients (n = 3)		P-Value
	n	%	n	%	
Age (Mean ± SD)	41 ± 12		41 ± 16		0.784
Height (Mean ± SD)	152 ± 17		155 ± 9		0.079
Weight (Mean ± SD)	71 ± 20		68 ± 19		0.366
Diabetes					
Yes	11	24.4	0	0	
No	31	68.9	3	6.7	
Hypertension					
Yes	7	15.6	0	0	
No	35	77.8	3	6.7	
Anemia					
Yes	31	68.9	3	6.7	
No	11	24.4	0	0	
Blood Group					
O	18	40.0	1	2.2	
A	12	26.6	1	2.2	
B	11	24.4	1	2.2	
AB	1	2.2	0	0	

among non-vWD and vWD patients. The vWF: Ac mean ± SD (51.4 ± 6.3) and vWF: Ag Mean ± SD (93 ± 67) were significantly lesser in vWD patients with that of non-vWD cases (98.7 ± 22.6) vs (116 ± 42.4) (p = 0.027) (p = 0.032) respectively. WBC, ESR, MCV, MCH, Hemoglobin, platelet count, INR, PT, APTT and FVIII showed no significant difference among the groups (p > 0.05) (Table 2).

4. Discussion

Dr. Eric von Willebrand described the first case of von Willebrand disease (vWD) in 1926. Endothelial cells and megakaryocytes produce the vWF, which then goes through a series of complex posttranslational modifications. The vWF gene is located on chromosome 12's short arm (Swami and Kaur, 2017). The VWD divided into six categories based on genotypic, clinical, and laboratory phenotypic characteristics (1, 2A, 2B, 2 M, 2 N, and 3). Depending on the severity of the underlying FVIII deficiency, VWD is characterised clinically by mucocutaneous bleeding and less commonly, hemarthrosis and soft tissue hematomas (Gill et al., 2015). Von Willebrand disease (VWD) is treated by correcting both the primary hemostasis defect caused by an inherited deficiency of von Willebrand factor (VWF) and the secondary defect of factor VIII coagulant function (FVIII:C) caused by the loss of VWF-mediated binding and stabilisation of this intrinsic

coagulation factor in flowing blood (Mannucci, 2019). The new weapons available to clinicians to treat patients with VWD are adequate, at least in countries that can afford to have them. Overall VWD has a lower health-care burden than haemophilia, and a new estimate shows that the number of patients who need replacement therapy is one-tenth lower (Mannucci, 2019). Since pregnant women with VWD have a higher risk of postpartum haemorrhage if they are not treated, treatment options should be discussed early in the pregnancy. Because of the risk of bleeding for the potentially affected neonate, invasive delivery control with ventouse or rotational forceps should be avoided (Castaman and James, 2019).

Von Willebrand's disease is a common hereditary bleeding disorder characterized by the lack or ineffective supply of von Willebrand factor in blood, coupled with deficient clotting factor VIII. Most common vwd type is type 1, which manifests holding milder symptoms, and type 3 presenting the rarest and severe form. Mostly inherited, vwd also shows an acquired version out of any autoimmune disease. Main symptoms attributed to vwd is easy bruising, excessive gum or nose bleeds, abnormal heavy bleeding during periods aka Menorrhagia. A detailed medical and family history substantiating any inheritance, laboratory tests of vwd levels and clotting factor VIII accounts for diagnosis. Treatment aims at stopping or preventing bleeding episodes, Desmopressin being a major drug of choice. In addition, for menorrhagia cases in women,

Table 2
The comparison of laboratory variables between VWD and Non-VWD patients.

	Non -VWD Patients (n = 42)		VWD Patients (n = 3)		P-Value
	Mean	SD	Mean	SD	
WBC(×10 ⁹ /L)	7.2	2.9	6.3	0.70	0.57
ESR	47	36	24	10	0.27
MCV	72.1	18.7	74.8	17.8	0.81
MCH (pg)	25.2	4.2	24.1	7.0	0.68
Hemoglobin ((g/L)	72.2	52.9	71.5	21.7	0.98
Platelets (×10 ⁹ /L)	321	145	261	25	0.47
INR	0.85	0.43	0.95	0.61	0.79
PT (s)	16	6.4	14	6.0	0.89
APTT (s)	33	19	37	5	0.72
vWF:Ac (IU/dl)	98.7	22.6	51.4	6.3	0.02*
vWF:Ag (IU/dl)	116	42.4	93	67	0.03*
FVIII (IU/dl)	112	34.2	92	21.4	0.29

WBC:- White blood cells; ESR:-Erythrocyte sedimentation rate; MCV:-Mean corpuscular volume; MCH:-Mean corpuscular hemoglobin; INR:-International normalized ratio; PT:-Prothrombin time Hemoglobin A1C; APTT:- Activated Partial Thromboplastin Time; VWF:Ac:-Von Willebrand factor activity; VWF:Ag:- Von Willebrand factor antigen; FVIII:- Factor VIII; SD: - Standard Deviation.

* Statistically significant (P < 0.05).

Oral contraceptives containing oestrogen mostly found effective in reducing blood clots. Desmopressin (DDAVP) is an effective and economical therapeutic choice for most people with mild/moderate vWD. Replacement treatment with pure vWF-containing concentrates is suggested for individuals who do not react to DDAVP, respond insufficiently, or have contraindications to DDAVP. With limited diagnostic facilities and therapeutic options, vwd demands better medical surveillances, individual case studies, patient awareness-thus aiding better management and tackling of this clotting disorder. The study shows wide range of clinical features of bleeding in the respondents. For patients with von Willebrand disease (VWD), surgical procedures provide a major hemostatic challenge, and careful perioperative treatment is essential to reduce the risk of bleeding. Common indicators comprised epistaxis, gum bleeding, menorrhagia, and bruises among these patients. According to the study results, there is no family history of venous thromboembolism (VTE) in these patients. Among the three vWD patients, one patient had underwent hormonal therapy. The majority of Non-VWD patients belongs to O blood group 40% (n = 18) followed by A blood group patients 26.6% (n = 12), B group 24.4% (n = 11) and AB group 2.2% (n = 1). The vWD patients were shared among O, A, B blood group respectively.

5. Conclusion

Von Willebrand disease was found to be the second common hereditary bleeding ailment and coagulation defect among menorrhagia in females. It was unambiguously acknowledged that menorrhagia is a significant cause of iron-deficiency anemia and consequent morbidity. The present study helps to assess vWD in Saudi population using their hemostasis profiles. To assess the menstrual cycle of each patient, blood extraction and analysis for complete blood count, C - reactive protein, ESR, coagulation screening test (INR, PT, and aPTT), bleeding time & clotting time, hormonal status, factor VIII assay, Von Willebrand Factor assay was performed. The mean of vWF: Ac and VWF: Ag were significantly lower in vWD patients. WBC, ESR, MCV, MCH, Hemoglobin, PLT count, INR, PT, APTT and FVIII showed no significant difference among the groups. Further studies are required, as there are limited materials on vWD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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