MANAGEMENT OF MENORRHAGIA IN VON WILLEBRAND DISEASE

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INTRODUCTION and OBJECTIVES

von Willebrand disease (VWD) is a congenital bleeding disorder resulting from a quantitative or qualitative deficiency of von Willebrand factor (VWF), a plasma glycoprotein with essential platelet-dependent functions in primary hemostasis and a carrier for factor VIII (FVIII) in the circulation. Menorrhagia is a common clinical problem in VWD and management of this condition has traditionally been the domain of the hematologists. Women with VWD frequently have menorrhagia and report impaired quality of life and increased absence from school or work during menstruation. In this report we evaluated the ratio of menorrhagia and management of this condition in VWD.

PATIENTS and METHODS

Ege Hemophilia Center is among the biggest centers in Turkey which serves all regions in Country. There are 145 patients with VWD registered to our center (82 females, 63 males; mean age: 16,0 years; range: 1.5-28 years). 106 of these patients are type-1 (73%), 23 type-2 (16%) and 16 type-3 (11%) (**table.1**). Among 82 female VWD patients, 61 are type-1 (75%), 11 are type-2 (13%) and 10 are type-3 (12%). Bleeding severity was measured using the Tosetto Bleeding Score.

Table 1. Properties of VWD patients.

Total number of VWD patients	**145**
Male / Female	**63 / 82**
Mean age (year)	**16.0 (1.5-28.0)**
Types of VWD: Type-1	**106 (73%)**
Type-2	**23 (16%)**
Type-3	**16 (11%)**

RESULTS

Among the 82 female patients, 58 have menstrual cycles (70%). 32 of 58 patients have menorrhagia (55%). Of these patients, 22 are type-1 (68%), 5 are type-2 (16%) and 5 are type-3 (16%). When the ratio of menorrhagia was evaluated according to VWD types, it was 49% in type-1 (22/45), 63% in type-2 (5/8) and 100% in type-3 (5/5) (**table.2**). Based on the severity of menorrhagia, most frequent treatment options were tranexamic acid, desmopressin and VWF-containing factor VIII concentrates. Additionally, oral contraceptives were used in 9 girls (15%) with menstrual cycle disorders. Treatment modalities according to VWD types are indicated in the **table.3**.

Table 2. Properties of female patients with menorrhagia.

Number of female patients	**82**
Female with menstrual cycle	**58 / 82 (70%)**
Type-1	**45 / 58 (77%)**
Type-2	**8 / 58 (14%)**
Type-3	**5 / 58 (9%)**
Patients with menorrhagia	**32 / 58 (55%)**
Type-1	**22 / 32 (68%)**
Type-2	**5 / 32 (16%)**
Type-3	**5 / 32 (16%)**
Menorrh. frequency in types	
Type-1	**22 / 45 (49%)**
Type-2	**5 / 8 (63%)**
Type-3	**5 / 5 (100%)**

Table 3. Treatment modalities of menorrhagia in VWD.

VWD	Treatment		
	Tranexamic acid (+oral contracep.)	Desmopressin + tranexamic acid (+oral contracep.)	VWF concentrates + tranexamic acid (+oral contracept.)
Type-1	**9 (4)**	**11 (2)**	**2 (1)**
Type-2		**3 (-)**	**2 (1)**
Type-3			**5 (1)**

of bleeding disorders. Antifibrinolytic agents inhibit the conversion of plasminogen to plasmin, which inhibits fibrinolysis and, thereby, help stabilize clots. Tranexamic acid was approved for the treatment of heavy menstrual bleeding by the U.S. Food and Drug Administration in 2009. It can be given orally (15–25 mg kg^{-1} tds) or i.v. (10 mg kg^{-1} tds). Desmopressin acetate (DDAVP), a synthetic vasopressin analogue, increases endogenous FVIII and VWF. DDAVP causes VWF to be released from endothelial stores. The mechanism for the rise in FVIII was thought to be due to its consequent stabilization in plasma. It is usually given by slow i.v. infusion of 0.3 μg kg^{-1} over 20 min. A more concentrated solution (15 μg mL^{-1}) is also available for s.c. use. Additionally, intranasal DDAVP is available in a special concentrated preparation. Factor VIII:C and VWF levels increase to two to five times baseline with a peak at 60 min after the completion of i.v. infusion of DDAVP (90–120 min after s.c. and intranasal application). Recombinant factor VIII and vWF complex infusion are plasma-derived concentrates used to replace factor VIII and vWF, respectively.

DISCUSSION

Once a diagnosis of VWD has been established, a multidisciplinary approach to management, which involves obstetrician–gynecologists and hematologists, results in optimal treatment outcomes. Many treatment options are available for women with VWD and heavy menstrual bleeding, including hormonal and non-hormonal therapies. Studies in women with VWD and heavy menstrual bleeding suggest that the levonorgestrel-releasing intrauterine system may be effective for this population. Use of progestin-only contraceptives, such as medroxyprogesterone acetate; progestin-only pills; and the progestin implant, also may reduce menstrual flow in the setting

CONCLUSION

Women with VWD frequently have menorrhagia in need of treatment. Severe bleeding episodes can be controlled with VWF concentrates; depending on the VWD type, mild bleeding episodes usually respond to treatment with desmopressin. Other treatments that can reduce symptoms include fibrinolytic inhibitors and hormones for menorrhagia. In conclusion, the successful management of VWD with menorrhagia requires the combined expertise of gynecologist and hematologist, most likely in specialized centers such as hemophilia treatment centers.