

## An Adolescent With a History of Menorrhagia

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### Clinical History

**Patient:** A 15-year-old African-American female presented to the hematology clinic for management of von Willebrand disease (vWD) and a 1-deamino-8-D-arginine vasopressin (DDAVP, or desmopressin) challenge.

**Chief Complaint:** Menorrhagia, requiring as many as 8 to 10 sanitary pads per day during menses lasting up to 1 month at a time.

**Past Medical History:** Previous von Willebrand panel ordered by a gynecologist reported as follows: von Willebrand antigen:

39%; von Willebrand activity: 36%; and factor VIII: 51%. No surgeries or hospitalizations.

**Family History:** Mother with heavy menses lasting 5 to 6 days per month but requiring up to 20 sanitary pads per day. Maternal aunts with history of heavy menses; one aunt and maternal grandmother had hysterectomies due to dysfunctional uterine bleeding.

**Medications:** Recently placed on oral birth control pills by a gynecologist.

**Physical Exam:** Healthy-appearing female in no acute distress. Vital signs within normal

limits. Normal physical exam without evidence of abnormal bruising, hepatosplenomegaly, or lymphadenopathy.

**Laboratory Findings:** After great difficulty and multiple unsuccessful attempts, a phlebotomist obtained her blood via venipuncture while the patient turned increasingly anxious. Since it became too late to perform the DDAVP challenge on her first clinic visit, the hematologist decided to place a large bore IV needle overnight and have her return the following day for the DDAVP challenge. **Table 1** shows the multiple sets of test results from both days.

### Questions

1. What is von Willebrand disease (vWD)?
2. How do you test for vWD? What is the most likely diagnosis in this patient?
3. What is the likely explanation for the difference in laboratory values over the 2 days of testing?
4. Which factors can affect von Willebrand factor levels?
5. How does DDAVP work and in which patients is it contraindicated?

### Possible Answers

1. Von Willebrand disease (vWD) is the most common inherited bleeding disorder with an estimated prevalence of approximately 1% in the population. Von Willebrand disease is characterized by either a quantitative or qualitative defect

in the von Willebrand factor (vWF). Von Willebrand factor is synthesized in megakaryocytes and endothelial cells, is essential for platelet adhesion, and serves as a carrier protein for factor VIII (FVIII). VWF undergoes extensive modifications to render it active, including dimerization, glycosylation, sulfation, and eventually cleavage into high-, intermediate-, and small-molecular-weight multimers. The larger multimers are more biologically active as they carry more FVIII as well as offer more binding sites for platelets. Once fully processed, vWF is released and is either free in the circulation or stored in the alpha granules of platelets or Weibel-Palade bodies of endothelial cells. The half-life of plasma vWF is approximately 12 hours.<sup>1,2</sup>

Clinical manifestations of vWD include mucocutaneous bleeding such as epistaxis, oral bleeding, and menorrhagia. The diagnosis of vWD requires a personal history of bleeding as well as a suspicious family history and an abnormal von Willebrand

**Table 1\_Von Willebrand Panel Results**

	Von Willebrand Antigen Level	Von Willebrand Activity	Factor VIII Activity
<b>Reference Range:</b>	<b>50% to 150%</b>	<b>50% to 166%</b>	<b>50% to 186%</b>
First clinic visit	60%	56%	136%
Second clinic visit prior to DDAVP	32%	51%	69%
Two hours post-DDAVP	163%	218%	401%
Four hours post-DDAVP	150%	172%	340%

DDAVP, 1-deamino-8-D-arginine vasopressin

profile. There are 3 types of vWD that arise from defects in the vWF (types 1, 2, and 3). In addition, there are 4 subtypes of type 2 (2A, 2B, 2M, and 2N).<sup>1,2</sup>

2. If the clinical and family history is suspicious for vWD, laboratory workup should include a von Willebrand panel, which measures the amount of circulating von Willebrand antigen, vWF activity through the use of ristocetin, and FVIII activity. These measurements are expressed as a percentage of activity. Ristocetin is an antibiotic removed from clinical use after it was discovered it caused thrombocytopenia because it induces binding between vWF and platelets. In the ristocetin activity assay, patient vWF agglutinates normal platelets and the amount of activity is calculated based on a standard curve. Different methodologies exist to measure vWF antigen level depending on the clinical laboratory, and FVIII activity is measured in clot-based assays with FVIII-deficient plasma.<sup>1</sup>

Types 1 and 3 vWD are characterized by quantitative deficiencies of vWF. Type 1 (the most common type accounting for 80% of cases) is characterized by a mild deficiency. Type 1 vWD is caused by a variety of genetic mutations in the vWF gene, which resides in chromosome 12.<sup>2</sup> Patients with this subtype have a mild bleeding history such as menorrhagia as seen in this patient. A von Willebrand profile will reveal slightly decreased levels of vWF antigen, vWF activity, and FVIII. Type 3 vWD is characterized by severe bleeding due to the almost complete lack of vWF. As vWF is essential for the binding of circulating FVIII, very little FVIII is bound and protected from proteolysis in the plasma, resulting in decreased circulating FVIII activity. Thus, in addition to mucocutaneous bleeding, patients with type 3 vWD have clinical bleeding in the form of joint and muscle bleeds similar to hemophilia A.<sup>1</sup>

Type 2 vWD is characterized by qualitative defects in the vWF molecule. The key to diagnosing type 2 vWD is recognizing the disproportionately decreased vWF activity compared with the amount of antigen. Further testing is necessary to delineate among the type 2 subtypes. Multimer analysis by gel electrophoresis and the ristocetin-induced

platelet agglutination (RIPA) with decreasing concentrations of ristocetin are useful in classifying the type 2 subtypes (Table 2). In type 2A, vWF has a mutation in its protease cleavage site making it more susceptible to enzymatic degradation. Consequently, the patient's plasma lacks the more biologically active high- and intermediate-molecular-weight multimers. In type 2B, the mutation is due to a gain of function in platelet GPIb/V/IX binding site on the vWF making it more "sticky." This leads to increased vWF-platelet interactions with subsequent clearance of high-molecular-weight multimers and platelets from circulation, leading to mild thrombocytopenia (greater than 100,000/microliter). In type 2M, the mutation causes loss of function in the GPIb/V/IX binding site and decreased vWF-platelet interactions. In type 2N, the defect is a mutation in the FVIII binding site. Therefore, as vWF acts as the carrier protein for FVIII, this mutation results in FVIII deficiency but not decreased platelet binding capacity.<sup>1</sup>

**Most likely diagnosis:** Type 1 von Willebrand disease.

Given the decreased von Willebrand antigen level on this patient's second day of testing and consistent with her history of vWD, she appears to have type 1 vWD. Since she was taking oral contraceptives at the time she presented to the hematologist, this could account for the higher vWF level compared with the prior results obtained by the gynecologist.

3. Various factors affect vWF levels, which can increase as much as 2 to 5 times during stress, including exercise and illness. Levels have even been shown to fluctuate in the event of a syncopal episode.<sup>1</sup>

The effect of stress and systemic inflammation on vWF antigen levels was studied in a unique double-blinded placebo controlled trial. In this study, 10 healthy male volunteers received 2 ng/kg of IV endotoxin, which was followed by systemic inflammation, fever, and chills. After 4 hours, vWF antigen levels increased to 259% of baseline in the endotoxin group compared with no change in vWF in the placebo group. It took 7 days for vWF antigen levels to return to baseline.<sup>3</sup>

As seen in this adolescent, the anxiety of traumatic venipuncture was the likely cause for higher levels observed on the

**Table 2 Subtypes of von Willebrand Disease (vWD) and Laboratory Analysis**

	Normal	Quantitative Defect		Qualitative Defect			
		Type 1	Type 3	Type 2A	Type 2B	Type 2M	Type 2N
Bleeding history	None	Mild to moderate	Severe	Moderate	Moderate	Moderate	Moderate
Von Willebrand factor (vWF) antigen	50%–150%	Mildly decreased	Markedly decreased	Normal to mildly decreased	Normal to mildly decreased	Normal to mildly decreased	Normal
vWF activity	50%–166%	Mildly decreased	Markedly decreased	Lower than antigen	Lower than antigen	Lower than antigen	Normal
Factor VIII level	50%–186%	Mildly decreased	Markedly decreased	Normal	Normal	Normal	5%–15%
Ristocetin-induced platelet aggregation	Positive with 1mg/mL of ristocetin	Not indicated	Not indicated	Decreased with 1mg/mL of ristocetin	Present with less than 1 mg/mL of ristocetin	Variable/decreased	Not indicated
Multimer analysis	High, intermediate, and small bands	Not indicated	Not indicated	Absent high and intermediate bands	Absent high bands	Normal distribution	Not indicated

first clinic visit compared with the results on repeat testing the following day.

4. The mean normal plasma level of vWF is 1 U/mL (correlating to 10 micrograms/mL or 100% factor activity). However, there is a wide variation designated as “normal,” ranging from 0.5 to 2.0 U/mL (50% to 200%). This variation is the result of genetic and environmental factors.<sup>1</sup> One example of a genetic factor is the difference observed between ABO blood groups. Individuals with blood group O have approximately 25% less vWF than those of groups A, B, or AB.<sup>4</sup> Another difference is noted between ethnic groups: African Americans have more vWF than Caucasians.<sup>2</sup> Unfortunately, we do not know our patient’s blood type.

Feminine hormones can affect vWF and FVIII, which increase during pregnancy and oral contraceptives use. VWF fluctuates throughout the menstrual cycle with the lowest levels occurring between days 5 to 7 of menses. During the third trimester of pregnancy, vWF also increases 3- to 5-fold over baseline. Age affects vWF levels as well, as neonates have higher levels of both vWF and FVIII than adults.<sup>1,2</sup>

Von Willebrand factor can be decreased by a variety of medical conditions leading to acquired vWD through 3 main mechanisms<sup>2</sup>: 1) autoimmune inhibition or antibody-induced clearance of vWF; 2) increased clearance of vWF by shear-induced proteolysis; and 3) increased vWF binding to platelets or other cell surfaces.

Patients with autoimmune disorders such as systemic lupus erythematosus, lymphoproliferative disorders, and certain cancers may develop acquired vWD. Cardiovascular lesions such as a ventricular septal defect (VSD) or aortic stenosis may cause increase in shear stress which accelerates vWF proteolysis by ADAMTS-13. This can lead to a depletion of large vWF multimers and produce bleeding similar to type 2A vWD. Once the underlying condition is treated, the vWF multimer distribution normalizes. Increased vWF binding to cell surfaces also depletes large vWF multimers in the circulation. An inverse relationship between vWF multimer size and platelet count exists. A probable explanation for this may be that ADAMTS-13 cleavage of vWF is proportional to the number of platelet-vWF interactions. This may be the mechanism by which acquired vWD is observed in certain myeloproliferative disorders that result in thrombocytosis. Decreasing the platelet count can restore a normal distribution of vWF multimers.<sup>2</sup>

Acquired vWD occurs in other medical conditions through nonimmune mechanisms such as hypothyroidism. Certain drugs, such as ciprofloxacin, valproic acid, and griseofulvin, have also been associated with acquired vWD.<sup>2</sup>

5. For patients with type 1 vWD, daily intervention is not needed as this subtype is characterized by mild bleeding episodes. In the case of menorrhagia, oral contraceptives are usually indicated. If normal vWF levels are desired, such as for surgery or other medical procedures, therapeutic options include DDAVP and concentrates of vWF and FVIII, which increase vWF endogenously or exogenously, respectively.<sup>1</sup>

DDAVP (also known as desmopressin) is a synthetic analog of vasopressin and exerts its effects by causing release of

vWF from Weibel-Palade bodies within endothelial cells.<sup>5</sup> It does not cause vWF release from platelets.<sup>2</sup> As it is synthetic, it carries no potential risk of transmitting blood-borne infectious agents as compared with plasma-derived factor concentrates. DDAVP can be given intravenously (IV) or intranasally. If given IV, a dose of 0.3 µg/kg in 50 mL of normal saline infused over 30 minutes will increase plasma vWF and FVIII levels 3 to 5 times above baseline. The effect occurs within 30 to 60 minutes following IV administration and lasts for 6 to 8 hours. The same result can be obtained with concentrated intranasal products with peak effect within 90 minutes of delivery.<sup>1,6</sup> However, because some patients fail to mount an increase in factor level regardless of vWD type, DDAVP challenges are common in clinical practice prior to a therapeutic interaction. For these patients, plasma-derived factor concentrates are available.<sup>1</sup>

Increasing endogenous vWF levels is less desirable in type 2B. The vWF gain of function results in spontaneous platelet aggregation and worse thrombocytopenia. Although in type 2M the vWF’s binding site has undergone a loss of function mutation making it less reactive, DDAVP is able to mediate desired hemostasis. In type 2N, the FVIII binding site is altered and doesn’t allow for proper binding. Thus, DDAVP-induced release of abnormal vWF does not correct the hemostatic defect and normal vWD from concentrates is the best option.<sup>1,2</sup>

Exogenous vWF is available for patients with type 3 vWD, types 2B and 2N, and in types 1 and 2 who are minimally responsive to DDAVP. Two different vWF concentrates exist, and the appropriate dose must be individualized according to the patient’s clinical condition, plasma volume, and factor concentration in the plasma and in the number of units in the product. As this is a plasma-derived product, vWF concentrates have the potential to transmit blood-borne infections, although the likelihood is significantly lessened by manufactured virucidal methods such as heat and detergent treatment.<sup>6</sup>

Antifibrinolytic agents such as epsilon aminocaproic acid (EACA) and tranexamic acid are especially useful in the setting of mucocutaneous bleeding. Such agents decrease fibrin degradation from enzymes naturally occurring within secretions such as saliva or urine. Thus, these agents are useful to help control oral and urinary bleeding.<sup>1</sup> LM

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