

Menstrual Bleeding and von Willebrand's Disease

Case Study:

A 28 year-old white female sought care from her gynecologist for increased menstrual bleeding. When she reached menarche at age 13, her menstrual bleeding was heavy enough to keep her out of school for several days each month. She discussed her bleeding pattern with her mother and sister. They reassured her that the use of extra heavy tampons for the first three days was normal for the women in their family, going back at least as far as her maternal grandmother. She denied hematuria, GI bleeding or epistaxis. A few months before seeking further gynecologic work-up, she found that she again experienced severe menorrhagia associated with dysmenorrhea. She found that aspirin or ibuprofen alleviated the symptoms but exacerbated her bleeding. Over the ensuing few months her menses became progressively worse. She had flooding despite using extra duty tampons. She began to feel weak and sought care.

Her gynecologist found her to be anemic (hemoglobin of 8.2 g/dl) and iron deficient. Her pelvic exam was normal. Her PT, aPTT, fibrinogen, and platelet count were normal. Her factor VIII was 22%, von Willebrand factor activity 24%, and von Willebrand antigen 30%. She had a test dose of intravenous 1-deamino-8-D-arginine vasopressin (desmopressin or DDAVP) at 0.3 ug/kg. One-half hour later her factor VIII was 102% and von Willebrand factor activity was 97%. She subsequently used intranasal DDAVP spray on the first day of her period for the past three years. All her periods have since been normal as well as her hemoglobin and iron levels.

Reflections on the Case:

Mucosal bleeding such as menorrhagia is one of the more frequent manifestations of von Willebrand's disease (vWD) and may result in iron deficiency anemia. During pregnancy and while on birth control pills, factor VIII and von Willebrand factor increase. Deliveries, including cesarean sections when required, may be uneventful without excessive bleeding. However, medications that produce a platelet functional defect, such as ASA, frequently cause a previously asymptomatic von Willebrand patient to bleed. If the underlying coagulopathy is not recognized, unnecessary surgical intervention (e.g. hysterectomy) may occur.

Historical Perspective:

In 1926 Dr. Erik Adolf von Willebrand described a hemorrhagic diathesis in 24 of 66 members of a family from the Swedish Åland Islands. Many women in the original kindred described by Dr. von Willebrand died of hemorrhage from menorrhagia or childbirth. The new bleeding disorder was not sex linked, like hemophilia, but had an autosomal pattern of inheritance. He believed the clotting abnormality was due to a functional disorder of platelets combined with a defect of the vascular endothelium. Later in 1953 researchers discovered that patients with vWD were deficient in circulating levels of factor VIII. They suggested that the defect was a plasma protein distinct from factor VIII and designated the protein as von Willebrand factor protein (vWF). During the past two decades, it has been shown that vWF and factor VIII are products of separate genes located on different chromosomes and their abnormalities cause two distinct bleeding disorders, vWD and hemophilia A.

Prevalence:

The prevalence of vWD varies with the population studied and has been reported to be as high as 1%. It is the most frequent genetic bleeding disorder. There are no apparent racial or ethnic differences in the distribution of vWD in the population but this has not been well studied. There is no apparent sex predilection.

Clinical Presentation:

The disease is frequently mild so that many affected individuals are asymptomatic and fail to report or recognize their symptoms as being important. The disease may be discovered only when the patient is subjected to physical or surgical trauma. Symptoms of bruising and bleeding from mucosal surfaces are commonly reported. In vWD, epistaxis and easy bruising are common in children; hemarthroses and intramuscular bleeds are not. The disease may be discovered after a tonsillectomy, tooth extraction or after aspirin or NSAIDs administration. The incidence of menorrhagia in adolescent women is 50% to 75%. Getting up at night frequently to change pads, passing clots or evacuating clots from the vagina during urination are all symptoms of menorrhagia. The normal amount of blood loss during menstrual endometrial shedding is only 50 ml. A positive family history may support the clinical suspicion for the disease. It may be difficult to establish a diagnosis of vWD for several reasons. Functional and antigenic vWF levels in affected individuals overlap with normal ranges, and they fluctuate with ABO blood group, age thyroid function and pregnancy. In addition there is no single definitive functional assay for this highly heterogeneous disorder.

Pathophysiology:

Megakaryocytes and endothelial cells synthesize vWF. Megakaryocyte-derived vWF is stored in the alpha-granules of platelets, predominantly in the low molecular weight form. Endothelial derived vWF is stored in the Weibel-Palade bodies of endothelial cells and tends to be the high molecular weight form. The low molecular weight form is constantly secreted by the alpha-granules and is used as a carrier protein for factor VIII. The high molecular form, from the Weibel-Palade bodies, is released when thrombin and fibrin is formed following injury to the vascular endothelium. Plasma levels of vWF can be increased by a variety of endothelial cells stimuli associated with inflammatory states, exercise, estrogen administration, pregnancy and increasing age.

The level of vWF antigen production in normal individuals and patients vWD appears to be related to ABO blood groups. Individuals with blood group O have significantly lower levels of vWF antigen and an increased incidence of vWD than those with blood groups A, B or AB. The reason for this association is unknown, although it has been postulated that there is a linkage between genes coding of ABO blood group antigens and vWF production.

Von Willebrand factor acts as a bridge between the platelet and vessel wall when injury occurs. The lack of this factor results in impaired adhesion of platelets to exposed subendothelium in high shear vessels. The vWF circulates as multimers that range in size from 0.5 million daltons (the dimer) to 20 million daltons. The larger ones are probably the most effective in supporting platelet adhesion. VWF serves as a carrier protein for factor VIII in the plasma. When vWF is reduced, factor VIII is less stable and there is enhanced clearance of factor VIII, leading to variable and mild factor VIII deficiency.

Classification of von Willebrand's Disease:

There are three major types of vWD. Type 1, which accounts for 80% of the cases, is characterized by partial quantitative decrease of vWF antigen and factor VIII. Type 3 is very rare and has total quantitative loss of vWF. Type 2 accounts for approximately 20% of the cases and has four subtypes (2A, 2B, 2N and 2M). All type 2 vWD share a qualitative defect in the protein. Distinct mutations in the vWF gene corresponding to different functional domains for each type have been identified. The characteristics of each type are listed in the table below.

Features and types of von Willebrand's disease

Type	Incidence	Inheritance	Features	Multimers	Treatment
1	80%	Autosomal Dominant	Partial quantitative deficiency In vWF	Normal	DDAVP usually results in satisfactory increase in vWF
2A	15 - 20%	Autosomal Dominant	Qualitatively abnormal vWF	Absence of large and intermediate sized multimers	DDAVP causes rise in VIII but may require Humate-P concentrate
2B	<3%	Autosomal dominant	Qualitatively abnormal vWF	Absence of large multimers	DDAVP causes decrease in platelets, Humate_P preferred
2M	<3%	Autosomal recessive	Qualitative abnormal vWF causes lack of binding to platelet	Normal large multimers	DDAVP results in increase in vWF but may require Humate-P
2N	<3%	Autosomal recessive	Decreased affinity for factor VIII but normal binding to platelets	Normal	DDAVP results in increase in vWF but may require Humate-P
3	<1%	Autosomal recessive	Severe quantitative deficiency in vWF	Normal	No response to DDAVP, Humate-P required

Laboratory Evaluation:

One caveat concerning laboratory tests for vWD is that tests are notoriously variable. A reasonable starting point to screen patients that are suspected of having vWD is a platelet count, PT, aPTT and factor VIII level. These tests are done at Rex Lab. The Ivy bleeding time, although once considered an important part of the work up for vWD, has such variable results that a normal or prolonged time adds little to the evaluation. It is no longer recommended for use in screening for coagulopathies. Depending on the sensitivity of the reagents used in the aPTT, the result may be normal, even when the factor VIII level is as low as 20%. This was true in our patient case study described above. All of these tests may be normal in mild disease since levels of vWF and factor VIII wax and wane. If clinical suspicion is high or the preceding tests abnormal, then specific assays for vWD are indicated. Von Willebrand factor antigen (vWF:Ag) and von Willebrand factor activity assay/ristocetin cofactor activity (vWF:RcoF) are the two assays that are very helpful in establishing the diagnosis of the major types of von Willebrand's disease. It may be necessary to do further analyses, such as vWF multimer analysis and ristocetin induced platelet agglutination (RIPA) to allow for further diagnosis and classification. These specific tests are referred to UNC Hospitals Laboratory. They may be ordered as a panel called von Willebrand workup with multimeric analysis. The cost of the reference test is \$380.00

The in-vivo DDAVP stimulation test, either intranasal or intravenous, elevates blood levels of vWF and factor VIII within 1/2 hour after administration. This test should be used with extreme caution since DDAVP may exacerbate the thrombocytopenia of type 2B.

Therapeutic Options:

Treatment of patients with vWD is directed at normalizing vWF and factor VIII in plasma. Therapy consists of either stimulating the endogenous release of these factors with (DDAVP) or providing exogenous substitution with a factor VIII concentrate.

Mild or moderate types 1 and 2: DDAVP is effective in the management of traumatic bleeding and before surgery in some patients with mild or moderate type 1 and type 2A vWD. The intravenous administration of DDAVP at a dosage of 0.3 mg/kg over a 15- to 30-minute period causes the release of vWF from endothelial cell stores. The peak response usually occurs in 30 to 60 minutes and persists for up to 4 to 6 hours. Subcutaneous

administration of DDAVP has also been reported to be effective. Repeated DDAVP administrations over a 24-hour period are ineffective; tachyphylaxis follows depletion of the endothelial vWF store. A nasal DDAVP spray (300 g) can be used in the ambulatory treatment of patients with vWD, both for the management of bleeding episodes and as preparation for minor surgery. The side effects of intravenous DDAVP are generally mild, including significant water retention and, rarely, thrombosis. Myocardial infarction has been reported. Because of the variability of response to DDAVP, a patient should be given a trial infusion of DDAVP before undergoing a planned procedure to determine whether the patient has an adequate response. Epsilon aminocaproic acid (EACA), 3 g four times daily orally for 3 to 7 days, is also useful for dental procedures and minor bleeding events. **Aspirin or NSAIDs must be avoided.**

Moderate and severe types 2 and 3: Patients with type 3 vWD and with types 2A and 2B, which are more severe than type 3, generally require replacement therapy with Humate-P, a pasteurized intermediate-purity factor VIII concentrate that has a substantial amount of large vWF multimers, or with cryoprecipitate infusion containing vWF, factor VIII, and fibrinogen. Cryoprecipitate is generally not recommended unless testing or treatment can avoid the risk of viral contamination. Transfusion of normal platelets can also be attempted on the grounds that platelet vWF can be hemostatically effective.

Treatment during pregnancy Treatment is generally not needed during pregnancy in women with vWD. The plasma vWF level rises during the second and third trimesters but falls rapidly after delivery. Late hemorrhage may occur 2 to 3 weeks postpartum. DDAVP is not used before delivery because of the concern that it may initiate contractions. Patients with type 2B vWD may have worsening thrombocytopenia during pregnancy because of the increase of abnormal vWF in plasma.

Stephen V. Chiavetta, MD

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For further information, call the Laboratory (784-3040). Telephone extensions are: Pathologists' Direct Line (3201), Sharon Logue (Lab Director 2400), Robin Ivosic (Core Lab Manager 3053), Elaine Patterson (Core Lab Manager 3054), Jackie Okoth (Core Lab PM Manager 4248), Diane Young (Anatomic Pathology Manager 3888), Nga Moore (Customer Service Manager 3396), Kori Horsley (Customer Service PM Manager 4340).