von Willebrand Disease: A Common Pediatric Disorder

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One of the most common hereditary bleeding disorders is von Willebrand disease (VWD), with a prevalence of approximately 1% in the general population.\(^1\) The primary symptoms are ecchymoses (small hematomas in areas of trauma) and epistaxis.\(^2,3\) Menorrhagia is also common and thus VWD is diagnosed more often in women than in men, although VWD is equally prevalent in both sexes. The diagnosis is often overlooked because the symptoms are not severe and recognition of this disorder is usually important only at the time of surgery, particularly surgery involving mucosal surfaces (eg, ear, nose, and throat surgery or dental procedures). It is not uncommon for the diagnosis to be missed throughout childhood, adolescence, and young adulthood.

Several decades ago, VWD was a poorly characterized disorder and medical students were taught that patients with VWD had a long partial thromboplastin time (PTT) and a long bleeding time. We now know much more. For example, many patients with clinically significant VWD will have a normal PTT and bleeding time, and the best clue to the correct diagnosis is often a carefully obtained personal and family history.\(^2,3\) There are variant forms of VWD, and the most common form can usually be successfully treated with a nasal spray that increases the release of the body’s own von Willebrand factor (VWF) from its sites of cellular storage.

The previously uncertain etiology of VWD has evolved into a fuller understanding of the complexities of its pathogenesis. Only two kinds of problems lead to VWD—insufficient amounts of VWF or abnormalities in the functional structure of VWF that interfere with its function. However, there are different routes to each of these and this has led to the subcategorization of VWD into types based on pathogenesis. These differ in severity, laboratory results, and appropriate treatments.\(^2,3\)

### Clinical Manifestations

Only the most common (type 1) and the most severe (type 3) forms of VWD are discussed in this section. Unusual clinical symptoms associated with some of the other variants are discussed later in this article.

The primary clinical symptoms of VWD are mucocutaneous bleeding (eg, epistaxis, gingival bleeding, bleeding after tonsillectomy or adenoidectomy, or bleeding after dental extraction),
menorrhagia, ecchymoses, and hematomas. Most normal children have occasional episodes of epistaxis and active children commonly have small ecchymoses on the anterior tibial region of their lower extremities. However, the physician must ascertain whether the bruising and other clinical symptoms are commensurate with the degree of trauma. In the absence of major trauma, continuous bruising, bruising in nonexposed areas, or bruises larger than a silver dollar may signify the need for a diagnostic workup.23

In some areas of the country, otolaryngologists obtain preoperative hemostasis testing for patients who will undergo tonsillectomy, adenoidectomy, or both. Although the relative merits of such screening are debatable, prolonged PTs, prolonged bleeding times, or abnormal clinical histories often prompt referral to a pediatrician or a pediatric hematologist. Patients who have undergone tonsillectomy or adenoidectomy and exhibit excessive intraoperative or postoperative hemorrhage are also commonly referred.

Because both VWF and factor VIII are “acute-phase reactants,” stress will increase their concentrations in plasma.4 Sometimes this elevates abnormally low levels of these proteins to the normal range. Patients with mild VWD and an acute surgical abdomen may not bleed because the stress of the disease and the surgery elevates the level of VWF sufficiently to minimize bleeding symptoms. In contrast, mild surgical procedures or procedures involving the mucosal surfaces where fibrin clots are lysed quickly often initiate hemorrhage. Thus, if one is evaluating a patient in the immediate postoperative period, a normal to low—normal result on the VWF assay may not rule out the diagnosis of VWD.2

Menorrhagia is a common symptom among girls and women. However, a careful history will often elicit other hemostatic symptoms in these individuals and serve as a basis to evaluate for VWD.

Patients with type 3 VWD have much more frequent and severe symptoms and are usually diagnosed at an earlier age. As we discuss later in this article, VWF is essentially absent rather than reduced in type 3 VWD, and because VWF acts as a carrier protein that protects factor VIII in plasma, factor VIII levels are usually less than 5% of normal. Thus, bleeding problems will be similar to those of patients with moderately severe hemophilia A. Patients with type 3 VWD will bleed at the time of any surgical procedure and are even at risk for spontaneous or trauma-induced intracranial hemorrhage. Because these patients do not make VWF, they must be treated with replacement of VWF and factor VIII.

**PATHOGENESIS**

**The Genetics of VWD**

The gene for VWF is located on chromosome 12. The mild forms of VWD are associated with an abnormality in only one of the two VWF alleles. Patients with severe type 3 VWD have abnormalities of both VWF alleles. Usually this results in no VWF being synthesized, which reduces the levels of factor VIII to near zero. However, the factor VIII gene is normal and only the survival of factor VIII is affected. We now know that a variety of modifying genes can alter the level of plasma VWF, independent of the VWF gene itself. For example, patients with blood group O have plasma levels of VWF that are approximately 30% lower than those of patients with other blood groups, although their VWF genes may be similar.

**The Functions of VWF**

VWF is produced in two types of cells—the endothelial cell and the platelet or megakaryocyte.23 The bulk of plasma VWF is derived from endothelial synthesis. Although secretion of VWF is regulated by both types of cells, only the endothelial cell can be induced to pharmacologically release VWF to ease clinical symptoms. This occurs as follows.

When a blood vessel is damaged during routine trauma, the endothelial layer is disrupted and the subendothelium exposed to flowing blood. Plasma VWF binds to the exposed subendothelium (collagen and other proteins) and is presumed to undergo a conformational change from a globular to a linear protein. This linear form of VWF is then capable of binding to circulating platelets and initiates the adherence of these platelets to the site of the damaged endothelium.

VWF has a second major function, which is to protect coagulation factor VIII (anti-hemophilic
factor) from intravascular degradation and to serve as factor VIII's carrier protein in plasma. The precise nature of the coordinate delivery of VWF and factor VIII to sites of hemostatic need is not yet fully understood. However, when platelets adhere to VWF, they become activated, and activated factor VIII, which has dissociated from VWF, assumes its regulatory hemostatic role on the surface of activated platelets. This factor VIII serves as a regulatory cofactor in the ultimate generation of the fibrin clot. Thus, this complex of VWF and factor VIII serves an important regulatory role in maintaining normal hemostasis.

The VWF Molecule

It is difficult to understand the various tests for VWD without first understanding the structure of VWF. One important point is that VWF is synthesized as a multimeric protein (ie, its product is linked to form larger molecules of varying sizes).

The larger the VWF molecule (higher molecular weight multimers), the more effective it is in regulating hemorrhage. It has also been suggested that if the VWF is abnormal and larger than normal, it may initiate abnormal platelet adhesion and cause a "thrombotic-like" condition such as thrombotic thrombocytopenia purpura. The VWF molecule has some regions within each of its building blocks that bind to factor VIII, and other regions that bind to platelets and subendothelium.

Genetic mutations may affect any one of these functions and in several ways. For example, mutations may result in a molecule that is decreased in concentration, does not correctly bind factor VIII, does not adhere to the subendothelium, or binds abnormally (either increased or decreased binding) to platelets. Thus, laboratory evaluation of VWF requires measuring its concentration, its structure, and its function. Because interpreting these assays requires extensive knowledge of VWF function, patients with mild or severe bleeding disorders are usually referred to a pediatric hematologist for a definitive evaluation.

LABORATORY TESTS

Although older textbooks suggest that the screening for VWD can be achieved using a bleeding time and a PTT, we now know that results of these tests may be normal in many, if not most, patients with VWD. These screening tests and the more specific tests for VWF are discussed below in greater detail.

Partial Thromboplastin Time

The PTT is abnormal in VWD only because factor VIII is reduced, secondary to the reduced VWF. Thus, reductions of VWF that are low enough to result in abnormal platelet adhesion may not be low enough to produce a sufficiently reduced level of factor VIII or a prolonged PTT. Therefore, many patients with VWD have normal PTs.

Bleeding Time

Although many physicians use the bleeding time as a screening test, it is subject to significant variability among laboratories and among individuals performing the tests. This test is less reliable in children who become agitated by the procedure and are unable to hold still. Even if the test is done under carefully controlled conditions, many patients who will subsequently be diagnosed with VWD will have normal bleeding times.

Having both a normal PTT and a normal bleeding time does not rule out VWD. If the clinical symptoms warrant further evaluation, specific tests for VWD should be undertaken.

VWF Antigen

VWF antigen is a quantitative measure of the VWF protein. The most common form, type I, is associated with a reduction of VWF protein because one of the VWF alleles is not functioning. As mentioned earlier, blood type significantly affects the plasma level of VWF so that patients who are blood group A and have 50% levels of VWF may have minimal symptoms and not seek the attention of a physician. In contrast, individuals who are blood group O are more likely to seek physician attention because their levels of VWF are lower. Many laboratories have established different normal ranges for different blood types.

One must also recognize that a low level of VWF, irrespective of whether the gene is normal or abnormal, determines whether the patient has bleeding symptoms. Thus, a person with a low
level of VWF may have bleeding symptoms in the absence of an abnormal VWF gene. For example, patients with hypothyroidism may have reduced levels of VWF and clinical bleeding even though their VWF genes are normal.

**VWF Function**

The function of VWF is determined by its ability to interact with platelets. In the common type 1 VWD, the reduction in function will usually parallel the reduction in protein. In some of the VWD variants that are discussed later, the interaction with platelets is reduced to a greater degree than would be expected from the reduction of VWF protein. In the laboratory, we most commonly measure this function as ristocetin cofactor activity. An antibiotic long removed from the marketplace, ristocetin causes VWF to bind to platelets and is thus a measure of platelet binding to VWF.

Another measure of vWF function is its ability to bind to collagen. As mentioned earlier, collagen and platelets are bound at different sites on VWF, so patients who have reduced platelet binding may have perfectly normal collagen binding. Nevertheless, laboratory tests can measure collagen binding of VWF. Both ristocetin cofactor assays and collagen binding assays are adversely affected by a reduced size of the VWF multimers.

**VWF Multimers**

This test measures the structural integrity of VWF multimers. If patients have VWF multimers that are smaller than normal, they will have abnormal VWF function with reduced platelet binding, collagen binding, or both.

**Factor VIII**

Because VWF serves as a carrier protein that protects plasma factor VIII, identification of a reduced plasma concentration of factor VIII may be indicative of a VWF molecule that has reduced factor VIII binding or a low level of VWF causing a secondary reduction of plasma factor VIII. Sometimes such patients can be incorrectly labeled as having mild hemophilia A.

Patients with type 1 VWD will have reduced levels of VWF antigen and ristocetin cofactor. However, variants of VWD can be associated with a decrease in protein, platelet adhesion, and binding to factor VIII, and an abnormal VWF structure. Consequently, the battery of tests described previously are usually offered as a panel to rule out the presence of VWD.

**THE CLINICAL SYNDROMES (Figure)**

**Type 1**

Type 1 is the most common form of VWD and accounts for more than 80% of cases. Symptoms are often mild and become clinically significant with only certain types of surgery or certain types of trauma.

The one group that should be diagnosed aggressively includes pubescent adolescent girls with menorrhagia. Most girls learn the definition of normal menstruation from their mothers, who may have undiagnosed VWD. Thus, simply asking whether menstrual periods are “normal” is insufficient. Additional questions should be asked (e.g., “Is there breakthrough bleeding at night?”, “Does menstrual protection require frequent changes during the day?”, and “Has the bleeding ever been heavy enough to cause iron deficiency anemia?”).

The severity of bleeding at menarche is also critical. Menarche is assumed to be associated with irregular and heavier menstrual bleeding. However, retrospective studies of women with VWD show that abnormal bleeding can be traced back to menarche.

**Type 3**

Type 3, also referred to as severe VWD, results from both VWF alleles being abnormal (homozygous). Because symptoms are severe, type 3 is usually diagnosed during infancy or early childhood. Because ecchymoses and hematomas are nearly always present, physicians are often incorrectly concerned about physical abuse. The presence of small hematomas in the center of small ecchymoses is evident in patients with type 3 VWD. In normal individuals, hematomas and ecchymoses only follow major trauma and are not small. If the extremities have tiny, quarter-sized bruises with central hematomas, a diagnostic evaluation should be undertaken. The blood loss from epistaxis in these children may be life-threatening. Appropriate instruction on how to apply pressure to the anteri-
### von Willebrand variants

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<th></th>
<th>Normal</th>
<th>Type 1</th>
<th>Type 3</th>
<th>Type 2A</th>
<th>Type 2B</th>
<th>Type 2N</th>
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**Multimers:**
- **absent**

**Figure.** Laboratory diagnosis of von Willebrand disease variance. VWF = von Willebrand factor; VWF:Ag = VWF antigen; VWF:Rco = VWF ristocetin cofactor; FVIII = factor VIII; Tx = treatment; conc = concentrate; DDAVP = desmopressin acetate; N = normal.

or nares can often control symptoms until medical attention is obtained. Elective or emergent surgery for children with type 3 VWD should be done under close, clinical, inpatient management using concentrates that contain VWF.

**Type 2A**

Type 2A is caused by the proteolysis of plasma VWF into smaller multimers. Because the large VWF multimers are absent, bleeding symptoms are often much more severe than in patients with type 1 VWD.\(^1\)\(^3\)

**Type 2B**

Type 2B is actually caused by an increase in VWF binding to platelets, especially by larger VWF multimers. This occurs spontaneously in plasma without the normal requirement of VWF exposure to the subendothelium through vascular injury.\(^2\)\(^3\) When this VWF binds to platelets, the platelets and the bound VWF are removed from the circulation by the spleen. Thus, these patients have mild to moderate thrombocytopenia. Clinical symptoms occur because the largest VWF multimers have been removed after binding to the platelet surface. Stress or pharmacologic agents that normally elevate levels of VWF may have the paradoxical effect of worsening the thrombocytopenia. Special clinical laboratory tests have been developed to measure this increase in platelet binding. The most common assay demonstrates that minimal concentrations of ristocetin cause agglutination of the patient’s platelets, but have no effect on normal platelets and VWF.

**Type 2M**

In type 2M, the binding of factor VIII is normal and the structure of the VWF (VWF multimers) is normal, but the ability to bind to
platelets is reduced or absent. The VWF antigen will be normal, although the VWF activity is markedly reduced (normal quantity, abnormal function).

**Type 2N VWD**

In type 2N VWD, the binding of factor VIII to VWF is reduced. This results in decreased survival of factor VIII and, therefore, a reduced plasma concentration. These patients must be differentiated in the diagnostic laboratory from patients with mild hemophilia A. This is usually done using a factor VIII binding assay to VWF. This condition is recessively expressed and results in clinical symptoms only if homozygous or where a 2N defect is on one allele and a type 1 defect is on the other allele. The platelet binding function is normal with this variant. Bleeding times are therefore normal unless the type 1 allele causes the VWF levels to be low.

**Other Forms**

Many other less common variants of VWD are described in pediatric hematology textbooks. Such rare variants are identified in only a few laboratories and are beyond the scope of this article.

**TREATMENT**

Most patients with type 1 VWD make structurally normal VWF in insufficient quantities. Because VWF storage sites exist within vascular endothelial cells, release of VWF from these storage sites can elevate the plasma concentration of VWF and decrease clinical symptoms in these patients. The released VWF and factor VIII generally have a normal 12-hour half-life. This release is accomplished by the administration of desmopressin acetate. Desmopressin acetate is a synthetic analog of vasopressin and is most commonly abbreviated as DDAVP (des-amino-D-arginine vasopressin). DDAVP can be administered intravenously, subcutaneously, and intranasally. The highest plasma levels are obtained by intravenous administration, but the ease of intranasal administration makes this route more acceptable. The dose of intravenous DDAVP is 0.3 μg/kg of body weight administered in 25 to 50 mL of normal saline during 20 to 30 minutes. A therapeutic trial is usually performed to prove that administration of DDAVP is effective. A 2- to 4-fold rise in the plasma concentration of both VWF and factor VIII is usually seen. During administration of DDAVP, oral fluids should be restricted to maintenance levels.

Intranasal DDAVP is available in several formulations, but only one can be used to adequately treat VWD. This formulation (Stimate, Aventis Behring, King of Prussia, PA) is administered at a dose of 150 μg (one puff) for children weighing less than 50 kg. For larger children or adults, 300 μg (two puffs) should be administered. If intranasal DDAVP is being given to treat the symptoms of epistaxis, the nose should be wiped free of blood before administration. If hemorrhage is brisk, absorption through the nasal mucosa is interrupted. This may warrant intravenous administration of DDAVP. Tachyphylaxis or progressive resistance to repetitive doses is sometimes identified. If repetitive doses are administered (usually not more often than every 12 to 24 hours), a measure of VWF response using a plasma assay may be warranted.

**Plasma-Derived VWF Concentrate**

The initial treatment identified for VWD 40 years ago was cryoprecipitate made from fresh frozen plasma, which was given intravenously when bleeding could not be controlled. This form of treatment is no longer recommended except in third-world countries or where VWF concentrate is unavailable.

VWF concentrate is produced from pooled, normal human plasma that has been fractionated and subjected to viral attenuation and purification. Currently, there is only one VWF concentrate licensed in the United States. This concentrate contains both VWF and factor VIII and is labeled with the number of ristocetin cofactor units. One unit per kilogram will increase the plasma concentration of VWF by 1.5%. Life-threatening bleeding requires the administration of 50 to 60 U/kg of ristocetin cofactor. Milder bleeding can be controlled by 20 to 30 U/kg. Such VWF concentrate is the only mode of treatment for patients with severe type 3 VWD who make no VWF. Because this concentrate contains some factor VIII, levels of factor VIII are increased after infusion but are not always as high as the levels of VWF.
Aminocaproic Acid

Aminocaproic acid is a pharmacologic formulation that inhibits fibrinolysis. Once a clot is formed, fibrinolysins assist in the normal healing process, but may be associated with rebleeding in patients with bleeding disorders. Thus, inhibition of this fibrinolysis by administering aminocaproic acid reduces the risk of rebleeding from mucosal surfaces. Aminocaproic acid will not benefit soft tissue bleeding. Its use for mucosal bleeding, particularly in the mouth, has been studied most extensively. The administration of topical or systemic aminocaproic acid is associated with a reduced need for VWF infusion therapy in patients with mucosal bleeding.10

Acquired VWD

Rarely, patients with autoimmune disorders such as systemic lupus erythematosus develop an autoantibody against VWF. In addition, rare patients have also been identified who had acquired VWD secondary to Wilms’ tumors or hypothyroidism. Acquired VWD is more common in adults, rarely occurring in children.2,3 Treatment of acquired VWD caused by an autoantibody may require special consultation with a pediatric hematologist.

CONCLUSION

VWD is a common hereditary bleeding disorder that affects males and females equally. Bleeding symptoms are primarily mucocutaneous. The diagnosis of VWD may require quantitation of VWF protein, analysis of its ability to bind to platelets, carry plasma factor VIII, or both, and determination of its structure. Mild forms can be treated by the administration of DDAVP, which will release endogenous stores of VWF and factor VIII. In patients with refractory symptoms or severe type 3 VWD, concentrates containing VWF are required to raise VWF to hemostatic levels. Particular emphasis is placed on the evaluation of the young girl with menorrhagia and the child with unexplained bruising. A careful clinical history is often the most sensitive indicator of this common hereditary condition.

REFERENCES