von Willebrand Disease

Description/Etiology

Von Willebrand disease (vWD) is a group of chronic bleeding disorders characterized by deficiency in or defective functioning of von Willebrand factor (vWF), a glycoprotein that carries factor VIII (FVIII) and promotes platelet adherence to endothelial surfaces to form clots. Except for a few individuals with acquired forms of the disorder, vWD imparts a lifelong tendency toward easy bruising, frequent epistaxis, and menorrhagia (i.e., excessive menstrual bleeding) in women. Bleeding ranges from mild to severe, with the potential for fatal hemorrhage.

There are three major types of congenital vWD. Type 1 vWD (an autosomal dominant trait characterized by vWF deficiency) can cause mild to moderate bleeding depending on the extent of the deficiency; it accounts for 60–80% of vWD cases. Type 2 vWD (characterized by functional vWF defects) is further classified into 4 subtypes: 2A (most common), 2B, 2M, and 2N. Type 2 accounts for 10–30% of cases, is usually autosomal dominant but can be autosomal recessive, and is usually of mild to moderate severity. Type 3 is the most severe form of vWD, and is characterized by complete vWF absence; it is rare (1–5%) and is an autosomal recessive trait. Rarely, acquired vWD develops secondary to Wilms tumor, congenital heart disease, or hypothyroidism.

Diagnosis of vWD is based on personal and/or family history of bleeding, clinical manifestations, and laboratory assays that quantify vWF levels and measure vWF activity. The differential diagnosis includes uremia, other platelet and/or clotting factor disorders (e.g., thrombocytopenia, Glanzmann thrombasthenia, afibrinogenemia, hemophilia A/B/C), myeloproliferative disorders, and drug-induced platelet dysfunction (e.g., due to aspirin).

Patients with only minor bleeding require no specific treatment. In more severe cases, medical treatment might be necessary to increase vWF level and reduce bleeding time. Desmopressin (DDAVP; a synthetic vasopressin analogue that stimulates release of vWF from endothelial storage sites) is first-line treatment for mild vWD. Patients who do not respond to DDAVP and patients with type 2B or type 3 vWD might require infusion of plasma-derived FVIII/vWF concentrate. Women with vWD and menorrhagia can benefit from oral contraceptives (e.g., progestin-only pills) or a levonorgestrel-releasing intrauterine system (LNG-IUS). Antifibrinolytics (e.g., tranexamic acid) can be ordered to prevent dissolution of hemostatic fibrin clots. Potential complications of vWD include postpartum hemorrhage (uncommon), gastrointestinal (GI) hemorrhage, hemarthrosis (i.e., bleeding into the joints), and delayed postoperative and/or oral cavity bleeding. Life expectancy is usually normal.

Facts and Figures

vWD is the most common hereditary bleeding disorder, affecting ~ 1–2% of the general population, or 1 in 100 to 10,000 individuals. Although vWD is thought to affect men and women equally, it is diagnosed more frequently in women because of menorrhagia, and it is more common among White women than Black women. In women with menorrhagia, 5–20% have undiagnosed vWD, and menorrhagia might be the only clinical manifestation of the disease. Among women with vWD treated with oral contraceptives, 85% report reduction in menstrual bleeding. More than 250 vWD-causing mutations have been
identified. Acquired vWD affects ~ 0.1% of the general population, including up to 21% of patients with aortic stenosis and 33% of those with polycythemia.

**Risk Factors**

Family history of vWD is the primary risk factor, but having a personal history of conditions that predispose a person to acquired vWD also is a high risk factor (for details, see Description/Etiology above). Consanguinity is common in kindreds with type 3 vWD. Risk factors for acquired vWD include intracardiac stress conditions, such as aortic stenosis, ventricular septal defect, and patent ductus arteriosus.

**Signs and Symptoms/Clinical Presentation**

Signs and symptoms of VWB include bleeding gums; epistaxis; easy bruising; menorrhagia; blood in the urine and/or stools; and prolonged bleeding after minor injury, dental work, or surgery.

**Assessment**

› **Patient History**
  • Assess for family history of a bleeding disorder
  • Assess for easy bruising, excessive mucosal (e.g., gingival), GI, postpartum, postsurgical, or postdental procedure bleeding, and/or menorrhagia

› **Laboratory Tests That May Be Ordered**
  • CBC can reveal ↓ Hgb and Hct levels, indicating anemia; platelet number and morphology will be normal, except in patients with type 2B vWD
  • Ristocetin cofactor assay, which measures platelet agglutination in response to the antibiotic ristocetin, will show reduced or absent levels of vWF
  • Immunoassay, radioimmunoassay, or ELISA will show reduced or absent levels of plasma vWF. vWF: CB ELISA reveals collagen-binding activity that helps in diagnosis and identifying the type of vWD
  • vWF multimeric analysis by gel electrophoresis will show the makeup and structure of vWF and help to identify the vWD type
  • Bleeding studies usually reveal ↑ bleeding time and ↑ PTT with normal PT/INR
  • UA might be positive for blood cells; stool samples might be heme-positive

**Treatment Goals**

› **Promote Optimum Physiologic Status and Reduce Risk for Complications**
  • Monitor vital signs and PT/PTT; observe for bleeding, decreased perfusion, and adverse reactions to blood products, if administered. Monitor fluid, nutritional, respiratory, and hemodynamic status
  • If bleeding occurs, elevate affected area and apply cold compresses and gentle pressure; assess for pain and administer prescribed analgesia
  • Administer prescribed DDAVP to stimulate vWF release from storage sites
  • Administer prescribed plasma products (e.g., Alphanate, Humate-P) to replace factor VIII, and vWF antifibrinolytics (e.g., epsilon aminocaproic acid) to inhibit fibrinolysis
  • Request referral to clinician specialists in hematology, surgery, and/or critical care if not already part of the treatment team

› **Provide Emotional Support and Educate**
  • Assess patient/family member anxiety level and coping ability; provide emotional support, encourage verbalization of feelings, and educate about the disorder, including individualized prognosis and the risks and benefits of treatment
  • Request referral to a mental health clinician for counseling on coping strategies, if indicated

**Food for Thought**

› Various factors affect vWF assays, including the patient’s ABO blood type; patients with type AB blood have 60–70% higher vWF levels than those with type O blood. Some laboratories interpret vWF levels based on specific normal ranges for each blood type
  
  In type 1 vWD, vWF level is strongly predictive of bleeding risk. This correlation is far weaker in type 2 vWD, where other variables such as platelet count and type of mutation play an important role in determining bleeding tendency. In patients with type 2 vWD, clinical history can provide more information about bleeding risk than laboratory test results indicating vWF level (Castaman, 2013)
In 50% of women undergoing hysterectomy for menorrhagia, no organic pathology is identified; some of these women might have undiagnosed vWD

Red Flags

- DDAVP can be harmful in treatment of type 2B vWD, causing thrombocytopenia and increased bleeding
- Cauterization and packing of the nose should be avoided to treat epistaxis in patients with vWD because bleeding frequently recurs after the clot falls off or the packing is removed
- Free-water intake should be restricted to reduce hyponatremia risk in patients treated with DDAVP, especially very young patients and adults > 65 years
- Suspicion of vWD can complicate investigation of child abuse. Although caregivers of children with vWD might be falsely suspected of abuse, vWD and abuse are not mutually exclusive; a vWD diagnosis does not automatically rule out abuse
- 15% of patients with type 3 vWD who have received multiple transfusions develop alloantibodies that inactivate vWF; they should be treated with recombinant FVIII because alloantibodies can cause life-threatening anaphylactic reactions

What Do I Need to Tell the Patient/Patient’s Family?

- Suggest asking the clinician for referral to genetic counseling if there is family history of vWD or other bleeding disorders, and/or if planning to have children
- Discuss the importance of wearing medical alert jewelry and/or carrying other identification of increased bleeding risk
- Advise women planning to become pregnant to inform the treating clinician
- Advise the patient to avoid drugs with known antiplatelet effects (e.g., aspirin, ibuprofen, naproxen, antihistamines, heparin, tricyclic antidepressants, calcium-channel blockers, high-dose penicillin)
- Emphasize the importance of immediate medical attention after minor injury and before surgical procedures (including dental procedures) to determine whether prophylaxis is necessary

References