von Willebrand Disease

Etiology and Overview[1,2]

- von Willebrand disease (VWD) is an inherited bleeding disorder in vast majority of cases but may be acquired in some cases. Most common hereditary bleeding disorder in US; affects up to 1% of general population (3.2 million, or 1 in every 100 people), with clinically relevant bleeding in approximately 1 in 10,000 people.[3]
- Usually autosomal dominant inheritance; occurs with equal frequency among men and women. Females commonly affected by symptoms: heavy menstrual bleeding or bleeding after childbirth.
- Caused by lack—due to deficiency or defect—of functional von Willebrand factor (VWF), a large glycoprotein in plasma and endothelium of a blood vessel, that is bridging molecule for platelet adhesion and carries factor VIII, a clotting protein, to site of injury.
- Classified into types based on blood levels of VWF and factor VIII activity; classification based on guidelines developed by VWF subcommittee of ISTH (International Society on Thrombosis and Haemostasis), published in 2006, and VWD expert panel of NHLBI (National Institutes of Health National Heart, Lung, and Blood Institute), published in 2007 by NHLBI.[4]
- Types of VWD[3]
  - Type 1: mildest and most common form (about 85% of cases), characterized by low levels of VWF (20% to 50% of normal levels) and/or factor VIII.
  - Type 2: normal amounts of VWF but impaired VWF function (qualitative abnormalities). Four subtypes: 2A (most common), 2B, 2M, 2N; treatment varies based on subtype.
  - Type 3: most severe and least common form (about 3% of cases); apparently due to inheritance of mutant *VWF* gene from both parents. Characterized by very little or no detectable plasma or platelet VWF and factor VIII.
- Wide variation in management, depending on VWD type, bleeding location, severity.
- Acquired VWD: due to development of antibodies to VWF. Can be associated with a variety of lymphoproliferative, myeloproliferative, and cardiovascular diseases; usually resolves with treatment of underlying cause.

New VWD Diagnosis and Management Guidelines in 2021

- In January 2021, four leading hematology organizations—ASH (American Society of Hematology), ISTH (International Society on Thrombosis and Haemostasis), NHF (the National Hemophilia Foundation), and the WFH (World Federation of Hemophilia) released comprehensive evidence-based guidelines to support patients and healthcare providers in their decisions related to VWD diagnosis[5] and management.[6]

- The new 2021 guidelines provide 19 recommendations on VWD diagnosis and management. Notably, they advocate for management of patients who experience bleeding but whose blood laboratory values do not meet current accepted thresholds for a VWD diagnosis. They also recommend routine VWD prophylaxis (injectable concentrate of clotting protein) several times weekly for VWD patients with frequent, severe bleeding negatively impacting their quality of life.[7]

Onset and Symptoms[8]

- Usually milder bleeding symptoms. Some patients with mild forms of VWD may not have any clinical symptoms.
- Characterized by mucocutaneous bleeding, including easy bruising, prolonged bleeding from a cut or laceration, frequent prolonged epistaxis and oral mucosal bleeding with dental procedures and extractions.
- In severe types of VWD, musculoskeletal bleeding, including muscle bleeds and hemarthrosis, may be sign/symptom.
- Heavy menstrual bleeding common among women, with periods lasting longer than 7 days, heavy menstrual bleeding after childbirth or miscarriage.

Diagnosis

- Bleeding assessment tools (BATs): ISTH BAT scores for VWD shown to correlate with disease severity but tests require expert administration. BAT scores higher in type 3 VWD compared with types 1 and 2, and higher in children with severe VWD (VWF:Ag < 10 U/dL) vs moderate VWD (VWF:Ag = 10–30 U/dL).[9]
- Diagnostic tests: Complete blood count (CBC; generally normal in VWD but patients with heavy or prolonged bleeding can have iron deficiency anemia); activated partial thromboplastin time (aPTT) test is measure of intrinsic pathway of clotting ability of factors VIII, IX, XI, XII (normal results of 25–40 seconds seen in mild VWD, slight elevation in about 50% VWD due to low levels of factor VIII); prothrombin time (PT) test of extrinsic pathway of clotting system (normal, 11.5–14 seconds); levels of factors I, II, V, VII usually in normal range.[10]
- These coagulation studies are complex to process and interpret.
  - Laboratory findings often fluctuate with hormonal influences in females; for example, medications such as birth control pills may alter results. (For females, best time to test is on first or second day of menses.)
  - Bleeding times can be prolonged by medications that interfere with platelet function (NSAIDs, aspirin, valproic acid). Tests for bleeding times or platelet function analysis (using PFA 100) are not usually done outside of designated specialty laboratories.
  - Because many factors (as well as difficult lab draws, difficulty in processing specimens) may affect laboratory findings, it is suggested that specialized coagulation studies be drawn at a designated coagulation laboratory.[11]
- Diagnostic tests: Factor VIII clotting activity (blood levels); VWF antigen (blood levels); measurement of VWF activity by ristocetin cofactor activity assay or newer, less variable platelet-binding assay, the VWF:GPIbM; structural analysis of VWF multimers; platelet aggregation tests (functional analysis); collagen-binding assays (especially useful for stratification of type 2 VWD based on differences in VWF function); genetic testing (may be helpful when type 2 VWD variant is suspected) done at specialty labs. Blood group O individuals have lower VWF levels.
- Platelet aggregation tests (functional analysis) may be warranted in the differential diagnosis of bleeding disorders.

Treatment and Patient Education

- Stable type 1 patients and some with type 2 VWD (but not type 2B) and acquired VWD who are not actively bleeding should receive trial of desmopressin, a synthetic analogue of vasopressin that stimulates release of VWF from endothelial cells, as well as factor VIII. Type 3 patients do not respond to desmopressin due to complete lack of VWF.
- Desmopressin dosing[12]: 0.3 mcg/kg administered intravenously or subcutaneously over 20 to 30 minutes every 12–24 hours. Desmopressin-generated VWF level of 30 IU/dL acceptable; 50 IU/dL ideal.
  - Stimate (intra-nasal desmopressin acetate– for home use) has been recalled and is currently not available. Estimated re-release date is second half of 2023.
  - Cautions on use of desmopressin: Prolonged use of desmopressin is associated with tachyphylaxis. In patients with cardiovascular or cerebrovascular disease, use VWF replacement therapy instead of desmopressin.
- Consider VWF replacement therapy (recombinant VWF; vonicog alfa) in type 3 disease (complete lack of VWF) or types 1 and 2 with severe bleeding not responsive to desmopressin/DDAVP.
- Mucosal bleeding: antifibrinolytic medications (synthetic lysine derivatives tranexamic acid and aminocaproic acid) to prevent fibrin clot breakdown.
- Heavy menstrual bleeding[8]: tranexamic acid. Hormone therapy such as oral contraceptives, which can increase blood levels of VWF and factor VIII. The Mirena progestin-releasing IUD has also been helpful for managing heavy menstrual bleeding.
- VWF replacement therapy should be considered for surgeries and procedures depending on extent of treatment needed.
- Life-threatening bleeding: Use VWF-containing products. May use cryoprecipitate and fresh frozen plasma if VWF products are not available.
- Patient education is essential to optimal management of VWD. It is important to review signs/symptoms and when to seek advice from a healthcare provider. Epistaxis care should be reviewed. Patients should be advised to avoid acetylsalicylic acid, ibubrofen, and medications containing these agents. Menstruating females should use a period-tracking app. The National Hemophilia Foundation and the World Federation of Hemophilia provide good educational materials.

Prognosis/Outlook

- Diagnosis and subclassification of VWD remain challenging but important advances in laboratory assays have deepened understanding of specific VWF functions, leading to improvements in diagnosis. Availability of recombinant VWF has improved management. The new 2021 guidelines for VWD diagnosis and management may lead to improved outcomes for patients with bleeding whose blood laboratory values are below designated thresholds currently used for a VWD diagnosis.
- Because patients with VWD require specialty care, they should be referred to a designated comprehensive hemostasis and thrombosis center (HTC) for possible suspicion of bleeding disorders or confirmed diagnosis. The Centers for Disease Control and Prevention website offers a list of designated HTCs.

References

1. von Willebrand disease. National Organization for Rare Disorders (NORD) Rare Disease Database.
2. Sabih A, Babiker HM. Von Willebrand disease. [Updated 2020 Nov 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.
3. von Willebrand disease. Centers for Disease Control and Prevention.
4. The diagnosis, evaluation, and management of von Willebrand disease. [full report] National Heart, Lung, and Blood Institute. US Department of Health and Human Services, National Institutes of Health. NIH Publication No. 08-5832. December 2007.
5. James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. *Blood Adv.* 2021;5(1):280-300.
6. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Adv.* 2021;5(1):301-325.
7. Organizations collaborate to develop international state-of-the-art guidelines on the diagnosis and management of von Willebrand disease. PR Newswire. January 12, 2021.
8. von Willebrand disease. National Hemophilia Foundation.
9. Sharma R, Haberichter SL. New advances in the diagnosis of von Willebrand disease. *Hematology Am Soc Hematol Educ Program* (2019). 2019(1):596–600.
10. Doherty TM, Kelly A. Bleeding disorders. [Updated 2020 Aug 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.
11. Jaffray J, Staber JM, Malvar J, et al. Laboratory misdiagnosis of von Willebrand disease in post-menarchal females: A multi-center study. *Am J Hematol.* 2020;95(9):1022-1029.
12. McCarty TS, Shah AD. Desmopressin. [Updated 2020 May 16]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.

Hemophilia

Etiology and overview

- Rare X-linked bleeding disorder affecting mostly males; in US, approximately 33,000 males living with hemophilia.[1]
- Hemophilia A (also known as classical hemophilia), is X-linked recessive genetic disorder affecting 1 in 5,000 males in US. It is most common congenital coagulopathy. All racial and ethnic groups equally affected. Severe disease seen in approximately 60% of hemophilia A patients.[2]
- Hemophilia B (also known as Christmas disease) is X-linked genetic coagulopathy affecting 1 in approximately 25,000 male births.
- Females may be asymptomatic carriers or have partial deficiency of specific coagulation factors; 10% to 25% have mild symptoms. Moderate and severe symptoms also reported in females with extreme lyonization.[3]
- Hemophilia A and B severity: severe: < 1%; moderate: 1%–4%; mild: 4%–50%.
- Hemophilia A: clotting factor VIII protein (factor VIII) deficiency, due to mutations of F8 gene. Inhibitor antibodies may develop in 30% to 35% with severe disease, usually within the first 50 infusions of factor.[4]
- Hemophilia B: clotting factor IX protein (factor IX) deficiency due to mutations of F9 gene. Presence of inhibitor antibodies very rare; may develop in 1% to 3%.[4]
- Hemophilia A can also be acquired (AHA); extremely rare, clinical presentations often acute with prolonged activated partial thromboplastin time (aPTT), characterized by autoantibodies against factor VIII. Affects men and women of all ages, with peak incidences seen in pregnant and older (> 60 years) patients. About half of AHA patients have autoimmune conditions or malignancy. Subcutaneous hematomas often first indication of disease. Due to disease rarity, comparative treatment studies not available; referral to expert centers is recommended for hematology expert care.[5] Patients should be referred to a federally funded designated treatment center.

Onset and Symptoms[2,3]

- Mild to severe, depending on levels of clotting factor in blood. Babies often diagnosed with circumcision or prolonged bleeding from a heel stick. Bleeding into joints and easy bleeding are characteristic symptoms. Menorrhagia can manifest among female carriers of hemophilia.
- Hemophilia A: Symptoms vary widely, ranging from mild to moderate to severe (with factor VIII levels ranging from 5% to 40%, 1% to 5%, and less than 1% of normal, respectively). Regardless of severity, bleeding episodes tend to be less frequent in adulthood.
  - Mild cases: Possible bleeding/bruising from mucous membranes (eg, nose, gums).
  - Moderate cases: May involve excessive bleeding after surgery or dental procedures. Spontaneous bleeding rare.
  - Severe cases: Spontaneous bleeding, often into deep muscles, joints (hemarthroses), causing joint pain, restricted movement.
- Hemophilia B: Similar to hemophilia A, symptoms can range from mild to moderate to severe (with factor IX levels ranging from 5% to 40%, 1% to 5%, and less than 1% of normal, respectively). Moderate cases may involve hemarthroses.
- Mild cases of hemophilia A may be undiagnosed until person has surgery or experiences an injury. Moderate hemophilia A often diagnosed before 5 or 6 years of age. Severe cases often diagnosed in infancy.
- Mild cases of hemophilia B may be undiagnosed until later in life, even adulthood. Moderate cases, like hemophilia A, often diagnosed before 5 or 6 years of age. Severe cases often diagnosed at birth or before 2 years of age.

Diagnosis[2,3,6,7]

- Diagnosis of hemophilia A and B informed by patient's personal and family history of bleeding and inheritance, as well as specific coagulation tests. However, there are cases of spontaneous mutation in about 1/3 of the new diagnosed individuals.
- CBC: generally normal, except in cases of unusually heavy or prolonged bleeding.
- Activated partial thromboplastin time (aPTT; measures clotting ability of factors VIII, IX, XI, and XII): prolonged in hemophilia A and B.
- Prothrombin time (PT; measures clotting ability of factors I, II, V, VII, and X): Results normal for most patients with hemophilia A and B.
- Elevated aPTT but normal PT/internal normalized ratio, bleeding time, and platelet count: Investigate levels of factor VIII, IX to determine disease severity.
- Clotting factor test results (levels of factor VIII or IX) and disease severity: 50%, mild hemophilia; 1% to 5%, moderate hemophilia; < 1%, severe hemophilia. (Factor VIII, IX levels in people without hemophilia range from 50% to 100%.)

Treatment and patient education[2,3]

- Desmopressin (delivered via injection or nasal spray increases endogenous factor VIII levels in mild hemophilia A.[8]
  - Stimate (intra-nasal desmopressin acetate– for home use) has been recalled and is currently not available. Estimated re-release date is second half of 2023.
- Replacement therapy: infusion of synthetic blood factors VIII and IX developed by laboratory-based cloning of specific clotting factors. Severe hemophilia A (FVIII ≤ IU/dL) may require multiple IV infusions weekly.
- Hemophilia A and B: Drugs that bypass effects of inhibitor antibodies in type A and type B, such as recombinant activated factor VII NovoSeven (r factor VIIa); Sevenfact (also r factor VIIa) approved April 2020 for treatment and control of bleeding episodes in adults, adolescents 12 y/o and older with hemophilia A or B with neutralizing antibodies.[9]
- Hemophilia A: Other medications used for treatment are FEIBA (factor eight inhibitor bypass activity) and Obizur (antihemophilic factor [recombinant], porcine sequence).
- Hemophilia B: Recommended treatment for bleeding is NovoSeven.
- Prophylactic treatment with recombinant factor VIII or recombinant factor IX to preserve joint and musculoskeletal function in men, young boys with severe hemophilia A and B.
- Nonfactor treatments for hemophilia A with/without inhibitors: emicizumab (monoclonal antibody, mimics factor VIIIa function).
- Mucosal bleeding: antifibrinolytic medications (synthetic lysine derivatives tranexamic acid and aminocaproic acid) to prevent fibrin clot breakdown.
  - Antifibrinolytic medications are *not* recommended in hemophilia with gross hematuria, due to risk of clot formation that may lead to ureteric or urethral obstruction.
- Symptom management for anemia if needed: iron supplementation, ferric carboxymaltose, blood transfusion.
- Patient education is also very important to optimal management of hemophilia. The National Hemophilia Foundation (NHF) and the World Federation of Hemophilia provide good educational materials, and local NHF chapters are good resources.

Prognosis/Outlook

- Significant advances in last decade, with extended half-life factor VIII and factor IX therapies, nonfactor replacement agents, and more recently, clinical trials of gene therapy for hemophilia types A and B.[10]
  - Clotting-targeted agents: Examples of agents currently under investigation include fitusiran (antithrombin small interfering RNA [AT siRNA] therapeutic) and monoclonal antibodies to tissue factor pathway inhibitor (TFPI), with concizumab furthest in clinical development.[10]
  - Nonfactor agents: HAVEN 2, largest prospective bleed prevention study to date in pediatric patients (88 males) with hemophilia A and factor VIII inhibitors, found once-weekly subcutaneous prophylaxis with nonfactor agent emicizumab improved health-related quality of life, with 77% of participants having no treated bleeding events.[11]
  - Gene therapy: The US Food and Drug Administration in January 2020 updated industry guidance on human gene therapy for hemophilia A and B.[12] Promising results of hemophilia B gene therapy were reported at 2020 American Society of Hematology meeting.[13]
- Because patients with hemophilia require specialty care, they should be referred to a designated comprehensive hemostasis and thrombosis center (HTC) for possible suspicion of bleeding disorders or confirmed diagnosis.
- The Centers for Disease Control and Prevention website offers a list of designated HTCs.

References

1. Soucie JM, Miller CH, Dupervil B, et al. Occurrence rates of haemophilia among males in the United States based on surveillance conducted in specialized haemophilia treatment centres. *Haemophilia*. 2020 May;26(3):487-493.
2. Hemophilia A. National Organization for Rare Disorders (NORD) Rare Disease Database.
3. Hemophilia B. National Organization for Rare Disorders (NORD) Rare Disease Database.
4. Meeks SL, Batsuli G. Hemophilia and inhibitors: Current treatment options and potential new therapeutic approaches. *Hematology Am Soc Hematol Educ Program*. 2016(1):657-662.
5. Tiede A, Collins P, Knoebl P, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. *Haematologica*. 2020;105(7).
6. Diagnosis of hemophilia. Centers for Disease Control and Prevention.
7. Doherty TM, Kelley A. Bleeding disorders. [Updated 2020 Aug 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.
8. Loomans JI, Kruip MJHA, Carcao M, et al. Desmopressin in moderate hemophilia A patients: A treatment worth considering. Haematologica. 2018;103(3):550-557.
9. FDA approves additional treatment for adults and adolescents with hemophilia A or B and inhibitors. [press release, FDA.gov] April 1, 2020.
10. Mannucci PM. Hemophilia therapy: The future has begun. *Haematologica*. 2020;105(3):545-553.
11. Young G, Liesner R, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. *Blood*. 2019;134(24):2127-2138.
12. Human gene therapy for hemophilia. Guidance for industry. US Food and Drug Administration Guideline Document. January 2020.
13. Gene therapy for hemophilia B found safe and effective in first phase III trial. American Society of Hematology. [press release] December 8, 2020.