Introduction to von Willebrand Disease

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OVERVIEW

Von Willebrand Disease (VWD) is the most common hereditary bleeding disorder in humans, with an estimated prevalence ranging upward to 1% of the general population. Males and females are both approximately equally affected. VWD arises from a deficiency or dysfunction of von Willebrand factor (VWF). VWF is a large multimeric plasma glycoprotein that has two key functions in hemostasis. First, VWF mediates the adhesion of platelets to the sites of vascular injury; second, it functions as a carrier protein that stabilizes blood clotting factor VIII within the circulation. Abnormalities in the ability of these two functions to be performed appropriately can lead to bleeding symptoms in affected individuals. These symptoms can include easy bruising, nose bleeding or epistaxis, oral bleeding, other mucosal bleeding such as heavy menstrual bleeding in women, or gastrointestinal bleeding. Affected individuals also may be at risk of bleeding following surgery, invasive procedures, traumatic injury, or childbirth.

There are three main variants of the disease. Type 1 VWD is a partial quantitative deficiency of normally functioning VWF. It is the most common variant, accounting for approximately 75% of symptomatic individuals, and is generally associated with mild bleeding symptoms. Type 2 VWD is a qualitative deficiency due to abnormal function of VWF. It accounts for nearly all the remaining affected individuals. Type 2 has further subtypes including 2A, 2B, 2M, and 2N. These subtypes are characterized by where the abnormal function occurs within the VWF. Of the subtypes, 2A is the most common. Type 3 VWD is the rarest of the variants and is estimated to only affect 1 in 1,000,000 individuals. It arises from the virtual absence of VWF protein and can be associated with severe bleeding symptoms.

Many types of VWD are inherited as an autosomal dominant trait in which an individual possesses a single gene mutation located on one chromosome of a pair (chromosome 12). Therefore a family history may reveal symptomatic bleeding within each generation. However, often there can be incomplete penetrance of the phenotype, accounting for variable expressivity of bleeding symptoms within families. Often there may not be a clear family history, particularly in milder forms of VWD. Type 3 and type 2N are known to have an autosomal recessive pattern of inheritance, and a family history can be negative. Type 2A and type 2M may be either dominant or recessive. VWD is significant for considerable heterogeneity of its molecular basis.

Molecular studies have been successful in identifying some genetic defects or mutations associated with type 2 and type 3 disease. However, studies of type 1 VWD have shown that the genetic basis of the type 1 disorder is highly variable and that defects in genes other than the VWF gene may also result in low plasma levels of VWF.

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Acquired von Willebrand syndrome (AVWS) is less common than hereditary VWD and often develops in conjunction with other medical disorders. Mechanisms that can lead to the development of AVWS include antibodies to VWF, shear- related conformational changes in VWF, increased blood platelet count, increased clearance of VWF from the circulation, and deceased VWF synthesis. This condition should be considered if the personal and family history are not suggestive of a congenital disorder.

HISTORY

In 1924, a 5-year-old girl who lived on the Åland Islands off the coast of Sweden was evaluated at Deaconess Hospital in Helsinki, Finland, by Dr. Erik von Willebrand for symptoms of epistaxis and ecchymosis. Her hematologic evaluation led to the discovery of the hereditary bleeding disorder that is now called VWD. In 1926, Dr. von Willebrand reported that this case differed from hemophilia in that mucocutaneous bleeding symptoms were exhibited, there was an autosomal inheritance within the family, a prolonged bleeding time using the Duke (or earlobe) bleeding time method was present, and there was a normal clotting time. He also found blood transfusions to be helpful in controlling the bleeding symptoms and treating the resultant anemia.

In the 1950's, the factor protein causing a long bleeding time in these patients was first called von Willebrand Factor. With the development of immunoassays and commercial FVIII concentrates, better understanding of the physical and functional separation of factor VIII and VWF was gained. In the 1970's, ristocetin testing to assess VWF qualitative function was initiated. In the 1980's, molecular advances were made, and the VWF gene was cloned in 1985. In addition, the classification or typing of VWD was started. In 1994, the International Society of Thrombosis and Hemostasis (ISTH) Subcommittee published the classifications of VWD, which were revised in 2006.

In 2008, the National Heart, Lung, and Blood Institute (NHLBI) published evidence-based clinical practice guidelines for evaluating and managing VWD. These guidelines are the first for any bleeding disorder and provide recommendations for clinical and laboratory evaluation of patients with a history of bleeding symptoms or medical conditions associated with increased bleeding risk with invasive procedures. They were developed for practicing primary care physicians, including family physicians, internists, obstetrician-gynecologists, pediatricians, and nurse practitioners, as well as hematologists and laboratory medicine specialists.

EVALUATION AND DIAGNOSIS

BLEEDING HISTORY

The initial step in evaluating a person for possible VWD or other bleeding conditions should focus on a personal history of excessive bleeding symptoms throughout one's life and any family history of a bleeding disorder. Bleeding symptoms common with VWD

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include epistaxis, menorrhagia in females, bleeding after dental extraction, ecchymoses, bleeding from minor cuts or abrasions, gingival bleeding, postoperative bleeding, hemarthrosis, and gastrointestinal bleeding. Symptoms are typically mild to moderate in severity and often involve the mucous membranes and skin sites, as type 1 VWD is the predominate subtype. More severe bleeding symptoms such as CNS or gastrointestinal bleeding can occur in persons with type 2 or type 3 disease but are rare in persons with type 1 disease. Hemarthrosis is an uncommon symptom and usually only occurs in persons with more severe disease, typically those with type 3 disease. Menorrhagia is a common bleeding symptom in both the general population and in women with VWD. However, the specificity of menorrhagia as a predictor of VWD is estimated at 5-20 percent. (1, 4) In adolescents with menorrhagia, the prevalence of VWD has been estimated at 3-36%. (11)

Bleeding symptoms are relatively common within the general population, and it is important to ask questions that can best identify persons who have a true bleeding disorder when taking a bleeding history. Several studies have used standardized questionnaires to compare responses from those already diagnosed with VWD to healthy controls. The following boxes are taken from the current National Heart, Lung, and Blood Institute (NHLBI) Guidelines to the Diagnosis, Evaluation and Management of Von Willebrand Disease. (1) They include questions to help determine which persons would most benefit from further diagnostic evaluation for VWD. (1, 2, 3)

Questions to Patient

1. Have you or a blood relative ever needed medical attention for a bleeding problem or been told you have a bleeding disorder or problem:
   - During/after surgery
   - With dental procedures, extractions?
   - With trauma?
   - During childbirth or for heavy menses?
   - Ever had bruises with lumps?
2. Do you have or have you ever had:
   - Liver or kidney disease, a blood or bone marrow disorder; a high or low platelet count?
3. Do you take aspirin, NSAIDs (provide common names), clopidogrel (Plavix), warfarin, heparin?

Box.1 Suggested Questions for Screening Persons for a Bleeding Disorder

1. Do you have a blood relative who has a bleeding disorder, such as von Willebrand disease or hemophilia?
2. Have you ever had prolonged bleeding from trivial wounds, lasting more than 15 minutes or recurring spontaneously during the 7 days after the wound?
3. Have you ever had heavy, prolonged, or recurrent bleeding after

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surgical procedures, such as tonsillectomy?

4. Have you ever had bruising, with minimal or no apparent trauma, especially if you could feel a lump under the bruise?
5. Have you ever had a spontaneous nosebleed that required more than 10 minutes to stop or needed medical attention?
6. Have you ever had heavy, prolonged, or recurrent bleeding after dental extractions that required medical attention?
7. Have you ever had blood in your stool, unexplained by a specific anatomic lesion (such as an ulcer in the stomach, or a polyp in the colon), that required medical attention?
8. Have you ever had anemia requiring treatment or received blood transfusion?
9. For women, have you ever had heavy menses, characterized by the presence of clots greater than an inch in diameter and/or changing a pad or tampon more than hourly, or resulting in anemia or low iron level?

Taking a bleeding history in the pediatric population can be difficult given the lack of hemostatic challenges experienced in young children. However, initial studies have demonstrated the utility of using a pediatric-specific tool entitled the Pediatric Bleeding Questionnaire (PBQ) to screen children for VWD. (7, 8) This tool was modified to include bleeding symptoms seen in young children such as umbilical stump bleeding, cephalohematomas, post-circumcision bleeding, post-venipuncture bleeding, and macroscopic hematuria. Bleeding scores greater than 1 on this questionnaire have demonstrated utility in predicting VWD in young children.

BASIC LABORATORY TESTING FOR VWD

Von Willebrand Antigen (VWF:Ag) measures the amount of VWF protein present in the plasma.

Von Willebrand function or ristocetin cofactor activity (VWF:RCo) measures the ability of VWF to interact with platelets through the use of the antibiotic ristocetin. Ristocetin causes VWF to bind to platelets; it was removed from clinical trials because it caused thrombocytopenia. It is now only used in laboratory testing to assess VWF function.

Factor VIII (FVIII:C) coagulant assay is used to assess FVIII activity and the ability of VWF to maintain the level of FVIII in the circulation.

VWF Multimers VWF is a large multimeric protein, and multimer analysis is a qualitative assay that shows the variable concentrations of the different sized VWF multimers. It is used to determine VWD subtype. It is typically performed after the initial panel (VWF:Ag, VWF:RCo, and FVIII:C) is positive for VWD.

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Ristocetin-induced Platelet Aggregation (RIPA) In type 2B there is increased binding of VWF to platelets. This can be detected by adding the antibiotic Ristocetin to platelets in the platelet aggregation test. This test is only done if there is a high suspicion of type 2B VWD (see below).

CLASSIFICATION OF VWD

Type 1: Partial quantitative deficiency of VWF. VWF:RCo levels and VWF:Ag levels are low. Typically the FVIII:C to VWF:Ag ratio is 1.5-2.0, resulting in a normal or slightly decreased FVIII level. (1) Multimers are normal.
Type 2A: Absent Multimers. VWF-dependent platelet adhesion is decreased with selective deficiency of high molecular weight multimers. Intermediate multimers may also be missing. This can be due to decreased assembly or increased proteolysis of multimers. VWF:Ag levels and FVIII:C levels may be normal or slightly decreased. VWF:RCo is moderately decreased. Multimer analysis shows decreased or absent high and intermediate molecular weight multimers.
Type 2B: Binding of platelets increased. VWF binding at the platelet GPIb binding site for VWF is increased, leading to increased platelet clumping and decreased VWF multimers and platelet numbers. VWF:Ag levels can be normal or slightly decreased, while VWF:RCo levels are moderately decreased. Multimer analysis shows a decrease of large multimers. There may be thrombocytopenia present in times of stress such as surgery or pregnancy. Laboratory analysis may be similar to type 2A or 2M. Further analysis by platelet aggregation testing will show abnormally increased Ristocetin- Induced Platelet Aggregation (RIPA) at low doses of ristocetin.
Type 2M: Multimers normal. VWF-dependent platelet adhesion is decreased due to abnormal binding of VWF to platelets at the platelet binding site GPIb. There can also be decreased binding of VWF to collagen. VWF:Ag levels can be normal or slightly decreased. VWF:RCo levels are moderately decreased. Multimer analysis can be normal with the high molecular weight multimers present.
Type 2N: Normandy. VWF binding to FVIII:C is impaired. FVIII:C levels are affected and may be less than 10%. Normal VWF:Ag and VWF:RCo levels are seen. To determine the difference between Type 2N and mild hemophilia A, assays of FVIII-VWF binding are performed. In addition, an autosomal recessive family history may be present.
Type 3: Virtually complete deficiency of VWF. VWF:Ag and VWF:RCo levels are undetectable, and FVIII:C levels are very low (1-9 IU/dL). No multimers are identified on multimeric analysis.

OTHER VWD-LIKE CONDITIONS

1. **Low VWF**. VWF levels ranging from 30-50 IU/dL pose a problem for making a clear diagnosis of VWD and determination of bleeding risk. Levels in this range may not be clearly associated with increased bleeding symptoms in all persons and do not show consistent linkage to changes in the VWF gene. ABO blood type O has been associated with low VWF levels: 80% of individuals with low VWF levels in the U.S. have blood type O. (1) Other reasons for low VWF levels in

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persons with a normal VWF gene sequence are not well understood. Persons with low VWF levels may have bleeding symptoms and may benefit from treatment to raise VWF levels. Therefore, persons with laboratory analysis of low VWF levels should be evaluated in light of their clinical and family picture.

2. **Acquired Von Willebrand Syndrome (AVWS)**. This is due to defects in VWF concentration, structure, or function that result from other medical disorders and are not inherited. Laboratory findings are similar to those in inherited VWD, including decreased VWF:Ag, VWF:RCo, and FVIII levels. Multimer analysis may be normal or may show a decrease in large multimers similar to Type 2A VWD.

GENETICS OF VWD

The VWF gene is located near the tip of the short arm of chromosome 12, at 12p13.3. It contains 52 exons and includes178 kb of DNA. VWD is a heterogeneous disorder and can be the result of a variety of molecular defects, including large gene deletions, frameshifts from small insertions or deletions, splice-site mutations, nonsense mutations causing premature termination of translation, and missense mutations affecting single amino acid residues. Unlike in hemophilia, no recurring large gene rearrangement that causes a large proportion of severe disease has been identified in VWD.

Many types of VWD are inherited in an autosomal dominant pattern. A clear family history may or may not be identified due to variable penetrance of the phenotype; bleeding symptoms can also vary within families. Type 2N and type 3 are known to be recessive in pattern and therefore may not be associated with a positive family history. In addition, 2A and 2M may be either recessive or dominant in pattern. Many of the mutations found in types 2B, 2M and 2N VWD are located in the DNA that directs the synthesis of specific regions of VWF. Common types of 2A VWD mutations can be found in the A2 domain of the VWF gene, while mutations producing less common types of VWD may be found throughout the gene.

Nurses working within the hemophilia treatment center (HTC) are engaged with patients who have inherited disease and participate in facilitating genetic testing and providing genetic information to individuals and families. A general overview of VWD genetics and current testing available is important, as molecular sequencing will likely continue to be an adjunctive approach to the diagnosis of VWD in the future. At this time, VWF sequencing has a clear role in the diagnosis of type 2N, differentiating between 2B and 2M, and potentially for use in family counseling of type 3. Given the complexity of the VWF gene and the amount of heterogeneity associated with type 1 disease, most genetic type 1 mutations have not been established. DNA sequencing is not practical for diagnosis of type 1, but continued advances may warrant testing in the future as several studies are attempting to characterize these mutations.

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MANAGEMENT OF VWD

Therapeutic management of VWD can be categorized into three general strategies. These strategies include methods to increase plasma VWF, first, through the use of nonreplacement medications, and second, through the administration of replacement VWF concentrates. The third strategy includes the use of other adjunctive medications that do not increase plasma VWF but promote hemostasis. In addition, there are some general medical management recommendations that are standard in patients with VWD. Specific of management of VWD with AVWS, menorrhagia, hemorrhagic ovarian cysts, pregnancy and childbirth will not be reviewed in this introduction.

ELEVATE VWF: NONREPLACEMENT THERAPY

The first strategy focuses on increasing the plasma concentration of VWF through the release of VWF stores within the body by the use of Desmopression Acetate or DDAVP. DDAVP is a synthetic derivative of the antidiuretic hormone vasopressin. DDAVP stimulates the release of VWF from endothelial cells where it is stored through the agonist effect of vasopressin receptors. DDAVP also causes the release of FVIII through mechanisms that are not completely understood.

Population studies have shown that most persons, including those with type 1 VWD, will have an increase of plasma concentrations of VWF and FVIII from twofold to fivefold over baseline levels after receiving DDAVP. Persons with type 2 disease will increase the plasma concentration of VWF following DDAVP administration, but these proteins will also retain their intrinsic molecular dysfunction. Therefore, laboratory and clinical monitoring are indicated to assess individual response in order to determine therapy plans. Persons with type 2B VWD can actually have worsening of their bleeding symptoms if given DDAVP, because the VWF released will cause thrombocytopenia due to clumping of platelets. Persons with type 3 VWD almost never demonstrate a rise in VWF:RCo or FVIII:C levels following DDAVP administration, hence it is not considered clinically useful in this subtype.

The standard dose of DDAVP based on maximal release data is 0.3mcg/kg given intravenously in 30-50ml normal saline over 30 minutes; peak levels typically occur 30-90 minutes post infusion. Most studies performed using 24- hour dosing have shown diminishing response to repeat dosing. The potential complication of hyponatremia with repeated dosing should be considered when determining therapy plans. Fluid restriction and sodium monitoring are recommended with repeated doses, particularly if DDAVP is used more than 3 times within 72 hours. If treatment is needed for greater than three doses, other strategies should be considered, including alternating use of DDAVP and VWF concentrate. Minor side effects of DDAVP include facial flushing transient hyper- or hypotension, headache, and gastrointestinal upset.

Intravenous administration of DDAVP is the preferred route of administration to prevent surgical bleeding, It is recommended that all patients with VWD undergo a therapeutic

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trial with measurement of VWF:RCo and FVIII:C levels pre and 1 hour post administration. This laboratory trial documents individual response to DDAVP and allows for effective individualized treatment planning.

Subcutaneous and intranasal administrations of DDAVP are also possible. Subcutaneous preparations are not currently available in the United States. The intranasal form, Stimate Nasal Spray for Bleeding, comes as 150 micrograms per metered nasal puff, with dosing recommendations for one puff for persons less than 50 kilograms and two puffs for persons greater than 50kg. Given variable nasal absorption, not all persons with a good intravenous response will respond to Stimate, and therefore a Stimate trial should also be performed.

Children under the age of 2 have been shown to have a lower response to DDAVP. (1) Seizure activity has been associated with hyponatremia caused by DDAVP, particularly in young children. Given this and the poor response rate, its use is not recommended in children under 2 years of age.

ELEVATE VWF: REPLACEMENT THERAPY

There are several licensed plasma-derived VWF concentrates available for replacement in persons with VWD. In the United States, these currently include Humate-P, Alphanate SD/HT, and Wilate. They are manufactured at U.S.-licensed facilities and are derived from pooled plasma from paid U.S. donors. They are purified products that undergo viral inactivation. It is important to note that these products have differing ratios of FVIII:C to VWF:RCo. They are typically dosed on the basis of VWF:RCo units per kilogram but can be dosed secondarily on FVIII units. Recombinant VWF is in clinical trials but is not yet commercially available.

Humate-P is indicated for use in adults and pediatric patients for treatment of spontaneous and trauma-induced bleeding or when use of DDAVP is inadequate. Humate-P has also received FDA approval for use in prophylactic management of surgery and invasive procedures in patients with VWD. **AlphanateSD/HT** is indicated for surgical and/or invasive procedures in patients with VWD in whom DDAVP is ineffective. It is not indicated for patients with type 3 VWD undergoing major surgery. **Wilate** is indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe VWD as well as in those in whom DDAVP is ineffective. It is not indicated for the prevention of excessive bleeding during and after surgery.

Replacement therapy with a VWF concentrate is indicated for significant bleeding events or major surgery in patients who have type 2 and type 3 VWD as well as for those with type 1 VWD who are unresponsive to DDAVP or require prolonged duration of therapy or where DDAVP is contraindicated. Dosing strategies for treatment typically consider VWD subtype, baseline VWF and FVIII levels, and type of procedure or bleed. A dose of 20-40 U/kg VWF:RCo can be effective for some minor procedures or bleeds; for major procedures or bleeds a higher loading dose of 40-60 U/kg VWF:RCo is used with maintenance dosing of 20-40 U/kg postoperative until wound healing is complete

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(usually 1-2 weeks). Continuous infusions have also been used successfully in surgical settings. Goals for treatment prior to minor surgery include achieving a VWF:RCo level greater or equal to 30 IU/dL and preferably greater than 50 IU/dL; this trough level should be maintained for 1-5 days. For major surgery or severe bleeding, goals of therapy should be VWF:RCo levels greater than 100 IU/dL with subsequent dosing to maintain levels above a trough of 50 IU/dL for 7-14 days. In DDAVP-responsive patients, DDAVP can be alternated with VWF concentrate to raise VWF plasma levels in the later part of treatment.

Adverse reactions to VWF concentrates are rare but can include allergic and anaphylactic symptoms, urticaria, chest tightness, dizziness, rash, pruritus, and edema. In persons with type 3 VWD and AVWS, inhibitor development is a possibility with exposure to VWF concentrates. These products should be used with caution in patients with known risk factors for thrombosis; it is recommended that FVIII levels be monitored to avoid unacceptably high levels if replacement therapy is given continuously for several days.

Long-term prophylaxis in VWD is not very common but has been implemented in some settings. Evidence-based guidelines have not been developed for this approach, but studies are being initiated to assess effectiveness.

OTHER THERAPIES

Adjunctive therapies to promote hemostasis are commonly used in VWD management. Antifibrinolytic drugs such as aminocaproic acid or tranexamic acid disrupt the process of fibrinolysis by inhibiting the conversion of plasminogen to plasmin. Through this inhibition, they stabilize blood clots that have formed.

Using antifibrinolytic agents in addition to DDAVP or VWF concentrates has been shown to be effective in controlling bleeding in the oral cavity and the gastrointestinal and genitourinary tracts. They can be used in persons with VWD to treat mild mucocutaneous bleeding and are available in oral or intravenous preparations. Aminocaproic acid (trade name Amicar) typically is administered every 6 hours for 5-14 days postoperatively. The dose is 50-100mg/kg every 6 hours with a maximum daily dose of 24 grams.

Intravenous tranexamic acid has been approved for use in the U.S. during and after dental procedures. The loading dose is 10mg/kg pre-procedure, followed by 10mg/kg every 6-8 hours for 2-8 days postoperatively. Oral tranexamic acid (trade name Lysteda) is now available in the U.S. and has been approved for use in women with heavy menstrual bleeding. The dose is 1,300mg every 8 hours for up to 5 days.

Aminocaproic acid and tranexamic acid are excreted renally; their use should be avoided in patients with hematuria or renal insufficiency. Side effects include nausea and vomiting; less frequently, thrombotic complications can arise. Contraindications include disseminated intravascular coagulation (DIC) and bleeding from the renal parenchyma or

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upper urinary tract, as reno-vascular thrombi as well as thrombi in the renal pelvis and lower urinary tract have occurred.

Topical agents such as fibrin sealant or bovine thrombin may be useful in persons with VWD during oral surgery. However, the use of topical agents as single or adjunctive therapies in VWD has not been proven. Topical use of plasma-derived products carries a potential risk of allergic and immune reactions.

General Medical Management Guidelines

Immunization to hepatitis A and B is recommended for persons with VWD, as they are likely to require human blood product administration. Also, education should be provided to avoid the use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and other platelet-inhibiting drugs.

REFERENCES

1. The National Heart, Lung and Blood Institute. The Diagnosis, Evaluation and Management of Von Willebrand Disease. Bethesda, MD: National Institutes of Health Publication 08-5832.2007. Available at http://www.nhlbi.nih.gov/guidlines/vwd.
2. The National Heart, Lung and Blood Institute. A Pocket Guide to the Diagnosis, Evaluation and Management of Von Willebrand Disease. Bethesda, MD: National Institutes of Health Publication 08-5833. 2008. Available at http://www.nhlbi.nih.gov/guidelines/vwd/vwd_pocket-gde.htm.
3. Nichols WL, Rick ME, Ortel TL et al.; Clinical and laboratory diagnosis of von Willebrand disease: A synopsis of the 2008 NHLBI/NIH guidelines. *Am J of Hematol*. 2009; 84: 366-370.
4. James AH, Manco-Johnson MJ, Yawn BP et al.; Von Willebrand disease; key points from the 2008 National Heart, Lung and Blood Institute guidelines. *Obstet Gynecol*. 2009; 114(3): 674-8.
5. Castaman G, Rodeghiero F. Advances in the diagnosis and management of type 1 von Willebrand disease. *Expert Rev Hematol*. 2011; 4 (1): 95-106.
6. Berntorp E. Prophylaxis in von Willebrand disease. *Haemophilia* 2008; 14 (Suppl. 5): 47-53.
7. Bujnicki HC, Sidonio RF, Kempton C et al.; Screening for von Willebrand disease in children: a case-control study. *J Thromb Haemost*. 2011; 9 (3): 1538-7836.
8. Bowman M, Riddel J, Rand ML et al.; Evaluation of the diagnostic utility for von Willebrand disease of a pediatric bleeding questionnaire. *J Thromb Haemost* 2009; 7:1418-21.
9. James P, Lillicrap D. The role of molecular genetics in diagnosing von Willebrand disease. *Semin Thromb Hemost* 2008; 24:502-408.
10. Riddel JP. Genetics of von Willebrand Disease type 1. *Biological Research for Nursing*. 2006; 8: 147-156.

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11. Mikhail S. Kouides P. von Willebrand disease in the pediatric and adolescent population. *J Pediatric Adolesc Gynecol* 2010; 23: S3-S10.
12. Paper R. Can you recognize and respond to von Willebrand disease? *Nursing*. 2003; 33(7): 54-56.
13. Karp S, Riddel J. Bleeding disorders. In *Primary care of the child with a chronic condition*, 5th edition. 2007, pp. 241-258.

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