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Von Willebrand Disease

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INTRODUCTION AND CLINICAL EVALUATION

One of the most common hereditary bleeding disorders, von Willebrand (vWD) disease affects 1-2% of the population.

When discerning whether a patient has vWD, it is *crucial to get a detailed bleeding history*. Patients with vWD usually experience muco-cutaneous bleeding symptoms including easy or unexplained bruising, nose bleeds, gum bleeding, prolonged bleeding after minor cuts, heavy menstrual periods and prolonged surgical bleeding, particularly after dental procedures, sinus surgeries, tonsillectomy or adenoidectomy. Careful attention should also be paid to a *patient's family history.*

CLASSIFICATION

There are three types of vWD with four subtypes: type 1, type 2 (type 2A, type 2B, type 2M, type 2N) and type 3. Determining what type of vWD a patient has is crucial in determining what course of treatment to follow.

Type 1 von Willebrand disease is the most common presentation affecting 80% of patients. It has an autosomal dominant inheritance and is considered a *quantitative deficiency*. vW antigen is present in lower levels and there also decreased functional activity. Additionally, factor VIII levels are also low.

Type 2 von Willebrand disease comprises 10-15% of all vW patients and is considered a *qualitative defect*. Due to its complexity and multiple possible mutations, type 2 vWD is broken into *four subtypes:*

Type 2A accounts for 10-12%, has an *autosomal dominant form of inheritance with a high penetrance and expressivity*. Patients with type 2A vWD usually experience moderate to moderately severe bleeding.

Type 2B affecting 3-5% of vW patients, is caused in majority by missense mutations. vWF has a higher affinity for GpIb on the platelet surface, resulting in mild thrombocytopenia. Patients with type 2B vWD are *not good candidates for DDAVP* because of the possibility of brief appearances of thrombocytopenia.

Type 2M is an uncommon presentation of VWD (1-2% of patients), characterized by a reduction in the binding of VWF to GpIb. This reduction results in a decrease in platelet adhesion.

Type 2N affects 1-2% of vW patients and characterized by lower FVIII level. It is an autosomal recessive disorder. Mutations in type 2N vWD mainly affect the N-terminus of the vWF within the FVIII binding site, resulting in decreased binding to FVIII.

Type 3 vWD is rare and affects at most 1% of vW patients. It is a homozygous or compound heterozygous disorder resulting from missense, nonsense, or frame shift mutations. Patients experience severe bleeding due to total absence of detectable vW factor. The FVIII activity is similar to that of the moderate hemophilia range (3-5%).

LABORATORY DIAGNOSIS OF vWD

In addition to a patient and family history, a diagnosis of vWD can be made through a series of laboratory tests.

Screening tests may demonstrate prolonged **closure time (CT) and activated partial thromboplastin time** (**aPTT**) however they are non-specific. A *full panel* may include FVIII:C, vW antigen, ristocetin cofactor (vWF:RCo), Ristocetin Induced Platelet Aggregation (RIPA), vWF multimer analysis, and less frequently collagen binding assay and vWF-FVIII binding assay.

vW antigen may be low in Type 1 vWD, unmeasurable in Type 3 disease, but may be normal or even elevated in Type 2 vWD.

FVIII:C is decreased in patients with vWD because of the loss of stabilization of FVIII due to decrease in vWF. In patients with type 3 vWD, FVIII:C is very low (1-5%).

Ristocetin cofactor (vWF:RCo) is one of the most sensitive tests used to diagnose vWD and is considered the standard method of measuring *vWF factor activity.* vWF:RCo indicates the linkage of vWF to the platelet glycoprotein Ib/IIIa receptors. In type 1 VWD, decrease in vWF:RCo are proportional to the vWF:Ag levels.

Ristocetin-Induced Platelet Aggregation (RIPA) is a measurement taken by mixing a patient's platelet-rich plasma with increasing concentrations of ristocetin. The majority of vWD subtypes are characterized by hypo-responsiveness to low strength ristocetin except for type 2B, characterized by hyper-responsiveness due to higher than normal affinity of vWF to the platelet GPIb.

vWF multimeric analysis is used to determine the subtype of vWD. The multimers are separated through the use of agarose gel electrophoresis and are reacted with polyclonal anti-vWF antibodies. The abnormalities revealed through the analysis of vWF multimers allows to determine the different subtypes of VWD.
Type 1 is characterized by normal sized multimers with decreased total antigen.
Type 2A is characterized by a lack of both large/intermediate molecular weight multimers.
Type 2B is characterized by absence of high molecular weight multimers.
Type 2M and 2N both express normal multimers.

The collagen binding assay (vWF:CB) measures the ability of vWF to bind to subendothelial collagen which allows for platelet adhesion and is determined through the ELISA of vWF binding to collagen on microtiter plates. Collagen binding assays are also available for testing the ratio of vWF:CB to vWF:Ag which can be used to help distinguish between type 1 and 2 vWD.

Factor VIII binding to vWF is used to distinguish type 2N vWD from mild/moderate hemophilia A. These results are reported as a ratio between bound vWF and FVIII. If a patient has type 2N vWD then this ratio would show a reduction.

Even with the following in depth diagnostic test, diagnosing a patient with vWD still has some ***pitfalls.*** Patients with mild type 1 vWD might risk being undiagnosed if testing performed during pregnancy, on OCP or estrogens. In addition, vWF is an acute phase reactant and can be elevated during inflammatory states or acute illness.

TREATMENT OF vON WILLEBRAND DISEASE
After a diagnosis of vWD, treatment can be discussed. A healthy patient with type 1 vWD is the best candidate for treatment with **DDAVP** (1-deamino-8-D-argine vasopressin) and might be asked to undergo a DDAVP challenge test. DDAVP is administered intravenously and works by elevating the FVIII and vWF plasma concentrations. During the challenge test, a patient will be given a therapeutic dose of DDAVP administered over 30 minutes IV at a dosage of 0.3 mcg/kg diluted in 50ml of normal saline. Baseline levels of vWF:Ag, vWF:RCo and FVIII:C will be measured and then repeated after DDAVP. A response to DDAVP is good if the FVIII and vWF plasma concentrations are raised 2-4 times that of the base level within 30-60 minutes. The increased levels of FVIII and vWF in plasma continue for 6-8 hours. These infusions can be repeated once daily for 2 days. If the medication is administered too frequently (more than three consecutive days), tachyphylaxis can occur.
Stimate (desmopressin) is a nasal spray used for the treatment of minor injuries, mucosal bleeding, menorrhagia, and can be used prophylactically for minor surgical procedures.

If a patient is not a good candidate for DDAVP, either due to a poor response or if the patient has a type 2B or type 3 vWD, physicians should consider administering factor concentrates, such as **Humate P**. Humate P is approved by the FDA for the treatment of all types of vWD. It contains the highest ratio of vWF:RCo:FVIII (2:1), also raising the number of high molecular weight multimers, and helping to increase platelet vessel adhesion. In addition to Humate P, Alphanate has been approved by the FDA for treatment of patients with vWD. Unlike Humate P, Alphanate has a lower retention of high molecular weight multimers with a ratio of 1:1 vWF:RCo, unlike the ratio of Humate P, which has a ratio of 2:1.

For dental procedures, antifibrinolytics such as **Amicar** (aminocaproic acid) can be used, given at a dose of 50-100mg/kg per dose every 6-12 hours for 3-7 days. It can be administered orally, intravenously or topically. Amicar is used for the prevention of bleeding from the oral cavity or for treatment of epistaxis. **Lysteda** (tranexamic acid) has also been approved for treatment of menorrhagia.

Oral contraceptive pills (OCP) have been used for the treatment of menorrhagia. OCP's increase the plasma levels of vWF and lessen the severity of menorrhagia in women with vWD.

CONCLUSION
vWD is one of the most common inherited bleeding disorders ranging from mild to severe in the presentation of symptoms. Gathering a detailed patient's and family bleeding history is the first important step in making a diagnosis and crucial interpretation of borderline laboratory results. False negative test results can be seen on OCPs, estrogens, during pregnancy, or acute illness. DDAVP challenge tests are used to determine whether DDAVP would be an acceptable method of treatment.

REFERENCES

1. Rodeghiero F, at al How I treat von Willebrand disease Blood 2009 114:1158-1165.

2. "The Diagnosis, Evaluation and Management of Von Willebrand Disease." Guidelines http://www.nhlbi.nih.gov/guidelines/vwd/3_diagnosisandevaluation.htm

3. Transfusion Medicine and Hemostasis: Clinical and Laboratory Aspects. Elsevier, 2009.

4. Practical Hemostasis and Thrombosis., MA: Blackwell Pub., 2005. 51-61.

5. Classification and Pathophysiology of von Willebrand Disease. http://www.uptodate.com/contents/classification-and-pathophysiology-of-von-willebrand-disease.

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