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## **Proceedings of UCLA Health**

### **Title**

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### **Permalink**

<https://escholarship.org/uc/item/0vc2t6b0>

### **Journal**

Proceedings of UCLA Health, 18(1)

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### **Publication Date**

2013-11-24

## CLINICAL VIGNETTE

# Diagnosis and Management of Von Willebrand Disease

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Von Willebrand's Disease is the most common inherited bleeding disorder. Low levels of Von Willebrand Factor are seen in about 1% of the population. However not all will have Von Willebrand disease, since presence of low level Von Willebrand factor alone is not enough to qualify as Von Willebrand Disease and other bleeding disorders are common in the general population<sup>1-4</sup>.

Von Willebrand Disease was initially described by Erik Von Willebrand in 1926, when he recognized that mucocutaneous bleeding was present in the individuals with normal platelet counts. We now know that Von Willebrand Factor is a nonenzymatic, multifunctional and multimeric protein that acts as bridging molecule between platelets and the vessel wall. Von Willebrand's Factor (VWF) is synthesized in the vascular endothelium and in bone marrow megakaryocytes. It is released from the endothelial surface in the vessel wall in response to injury. It then binds to GpIb receptor on the platelet surface causing platelet aggregation. It also binds to subendothelial structures such as collagen, forming a bridge between subendothelial structure and collagen in response to stress. It also binds to Factor VIII, stabilizing and extending the half-life of Factor VIII from 2 hours to 8 hours in the circulation.

When there is no injury or disruption of the endothelium, von Willebrand factor is present in plasma and in the subendothelial tissue. Normally, platelets are circulating in an inactive state and are contact with vascular endothelium. If von Willebrand Factor comes into contact with an intact vascular endothelium, no platelet activation takes place.

In the setting of a vascular injury, subendothelial von Willebrand factor is exposed to circulating platelets and binds to activated glycoprotein Ib alpha platelet receptor. This binding action exerts a torque on the platelet, and results in platelet activation. Consequently multiple platelet receptors are activated. Platelet secretion of intracellular contents, such as alpha granules,

leads to recruitment of other platelets and culminate in platelet adhesion and aggregation.

VWF is a protein that is assembled from identical subunits into linear strings of varying sizes, referred to as multimers. The multimers are very large structures, that can be as large as 20 million daltons.

Upon secretion, the ultra-large von Willebrand factor molecular weight multimer complexes, and undergoes physiologic proteolysis by a metalloprotease ADAMTS-13. It is necessary to have "larger multimers" for VW Factor to function properly, but if very large multimers are left in the circulation, spontaneous thrombosis can occur in the microvasculature as seen in TTP. In TTP, large VW Multimers bind to platelets and collagen, without apparent stimulus, or injury to the vessel wall .

The VWF gene has been identified, a very large 178kb gene with 52 exons. The gene is highly polymorphic, with more than 1,100 single nucleotide variants with more than 567 gene mutations already identified (<http://sheffield.ac.uk/vwf/index.html>)<sup>5</sup>. Gene sequencing may be useful in clinical decisions, such as identifying Type 3 disease, as large deletions may put patients at risk for developing antibodies. Individuals with Type 3 disease may need genetic counseling.

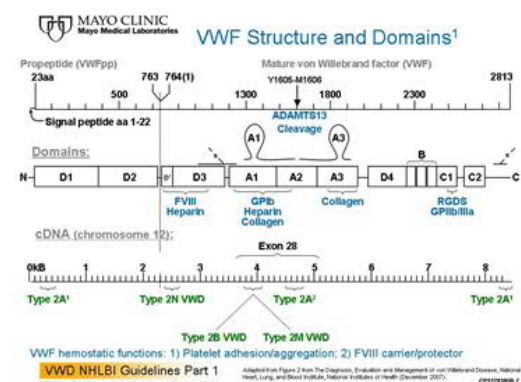


Figure 1

The VWF protein amino acid sequence, shown at the top of this diagram, is aligned with the VWF gene cDNA at the bottom, and domains of VWF are shown in the middle. Each subunit has specific domains for different ligands that bind to VWF: Factor VIII, collagen, heparin, platelet glycoprotein Ib complex, and platelet glycoprotein IIb/IIIa complex Type 2A, 2B and 2M mutations have been mapped to exon 28.

### **Diagnosis and Clinical Presentation**

Patients present with symptoms of mucous membrane bleeding such as epistaxis, menorrhagia, GI bleeding especially associated with angiodysplasia, as well as oral bleeding. On rare occasions patients may present with joint hemorrhages and bleeding early in life. The usual screening tests, such as PT, PTT, platelet count, bleeding time and PFA -100 are not always useful. If personal and family histories of bleeding are strong enough to raise the potential diagnosis of VWD, specific diagnostic tests should be ordered.<sup>4</sup> These include Von Willebrand Antigen, (VWF:Ag), Von Willebrand Factor Ristocetin cofactor activity (VWF:RCo), Factor VIII activity level (FVIII:C) and multimeric analysis.

These specific tests can be affected by additional factors: There is a physiologic difference in the levels of the Von Willebrand factor in patients with different blood types. For example individuals with type "O" Blood type will have VW levels about 25% lower than individuals with other ABO Blood types. Inflammation, adrenergic stimulation, estrogen replacement and pregnancy can increase VWF levels. Therefore before the diagnosis is made, individuals with borderline low VWF levels should be tested on three different occasions, several weeks apart.

### **Laboratory Testing**

**Von Willebrand Antigen Test** is a standard ELISA type assay, where antibodies are used against the Von Willebrand Antigens. **Von Willebrand Factor Activity** (Ristocetin Co-Factor Test) evaluates the functional ability of Von Willebrand Factor to bind to platelets, in the presence of Ristocetin, an antibiotic that promotes Von Willebrand Factor binding to platelets. The endpoint of the assay is clumping of platelets. In the assay, Ristocetin is added to

patient's plasma (a source of von Willebrand Factor) and normal platelets. With different concentration of Ristocetin a calibration curve is made, with a quantitative analysis of Von Willebrand Factor.

**Platelet Function Analyzer** is a surrogate for a bleeding time. The patient's own platelets and Von Willebrand Factor are used, so this is a test of platelet function, and is not specific to intrinsic Von Willebrand Factor levels.

**Factor VIII Activity** is performed using traditional Coagulation factor Assay. **Von Willebrand Multimer Assay** tests for the presence of large Von Willebrand Multimers in the plasma using electrophoresis on diluted plasma, in agarose gels. These multimers are crucial for adequate Von Willebrand binding activity.

**RIPA** testing is used to subclassify VWD, and to determine whether a gain of function mutation is present, which occurs in type 2B Von Willebrand Disease. Patient's plasma and platelets are added together (not the normal platelets that used in the Ristocetin Cofactor Assay) and platelet aggregation is assessed. Different concentrations of ristocetin are added to the mixture. Concentrations less than 0.6 mg/ml do not cause aggregation in normal subjects, but will cause aggregation if there is a gain of function mutation (Type 2B Von Willebrand's Disease).

Levels of VWF:Ag and VWF:Rco of <30 IU/dL are used as the cut off for diagnosis of VW disease. The cut off is low because, there is a high frequency of Type "O" Blood in the US, bleeding symptoms are reported by many individuals, no abnormality in the VWF gene has been identified in many individuals with mildly to moderately low VWF:Rco levels.

### **Classification**

VWD is divided into three types<sup>1-4</sup>.

Type 1 accounts for 75-80% of the cases and is due to a quantitative decrease in the Von Willebrand Factor. Laboratory testing shows: decrease in antigen and decrease in Ristocetin Cofactor activity multimers are normal, RIPA is decreased, Factor VIII is normal or slightly decreased. Patients usually have mild to moderate bleeding. Patients with type 2 VWD

represent 10-20% of all cases. They have mutations that impair functional domains. They have greatly reduced VWF:RCo/VWF:Ag ratio. Type 2A, 2B and 2M mutations have been mapped to exon 28.

Type 2A is a rare disorder that is due to the absence of large multimers. A mutation in the A2(2A<sup>2</sup>) domain makes the Von Willebrand molecule more sensitive to proteolysis by Adamts 13. The other mutation in Type 2A<sup>1</sup> causes abnormal multimer synthesis (Figure 1). Laboratory findings in type 2A include decreased Ristocetin activity more than the antigen because of the loss of more functional high-molecular weight-multimers, low RIPA with low/normal Factor VIII level. The high-molecular-weight multimers are absent on agarose gel. Patients have moderate to severe bleeding and present before adulthood.

Type 2B accounts for 5% of VWD. It is characterized by a gain of function mutation, where an abnormal Von Willebrand Factor has an increased affinity for G1P23b domain on the platelet surface. These complexes are cleared rapidly from the circulation, and therefore patients may have thrombocytopenia and moderate bleeding. Laboratory findings in Type 2B include abnormal RIPA, since low concentration of ristocetin cause platelet aggregation. There is a decrease in ristocetin Cofactor Activity and there is a decrease in High Molecular Weight Multimers. Patients have thrombocytopenia and moderate bleeding symptoms

Type 2M is very uncommon. It results from a mutation affecting the A1 domain (in different area than 2B). Laboratory findings in Type 2M are decreased VWF antigen and decreased Function (Activity). Multimer pattern is normal, although very large multimers (Vicenza variant) can be seen.

Type 2N (Normandie) is a rare disorder in which Von Willebrand molecule has a defect in the amino terminus end, where it normally binds Factor VIII. Due to the defect, Factor VIII's half life is decreased since it is not stabilized in the circulation by the Von Willebrand Factor. Platelet related Von Willebrand function is normal. Patients present with symptoms related to Factor VIII deficiency such as joint or soft tissue bleeding. Laboratory evaluation in Type

2N includes: normal Von Willebrand Antigen, Ristocetin Cofactor Activity and RIPA. Diagnosis is established by performing an assay, testing patient's VWF binding to factor VIII. This disorder can be confused with Hemophilia A, but affects males and females.

Type 3 VWD is a rare disorder (1-2 cases/million) characterized by almost complete absence of Von Willebrand Factor, and accompanied by moderate deficiency of factor VIII. This is usually due to larger deletions in the VW gene and is inherited in homozygous or double heterozygous manner. Laboratory Findings Type III include reduced von Willebrand Antigen and Ristocetin Cofactor Activity. Factor VIII activity is very low and multimers are not visualized. Gene Analysis may play a role in the diagnosis. Patients with Type III Von Willebrand Disease present early with severe bleeding.

### ***Treatment***

Treatment of VWD in the United States varies widely and frequently is based on local experience and physician preference. Few standard recommendations exist to guide therapy for VWD.

There are three types of treatment options for the patients with Von Willebrand Disease: DDAVP, replacement therapies with factor products as well as adjunctive therapies with fibrinolytic agents, such as aminocaproic acid or other agents that promote hemostasis or wound healing, but do not increase VWF concentrations. These options are not mutually exclusive<sup>5</sup>. Infusions of VWF to prevent bleeding episodes — known as prophylaxis are less frequently required in patients with severe VWD in contrast to patients with severe hemophilia.

Most of the patients with type 1 and Type 2 VWD can be treated with desmopressin . Desmopressin (DDAVP) is a synthetic derivative of the antidiuretic hormone, vasopressin. Desmopressin has been used to treat VWD for more than 25 years. The agent causes the release of the Von Willebrand factor and factor VIII from the endothelial surfaces, and can cause a 2 to 5 fold increase of both VWF and factor VIII. The effect takes place within 45 minutes and can last for 6 hours.<sup>4</sup>

It is extremely important to do a therapeutic trial of DDAVP before invasive procedures to demonstrate increase in the levels of VWF, and to document that there no resulting thrombocytopenia. DDAVP induced thrombocytopenia can be seen in type 2B disease following administration of DDAVP. VWF:RCo and FVIII activities should be measured in all VWD patients at baseline, and within 1 h and 2-4 hours after administration of desmopressin. Decrease in platelet count after desmopressin has been considered "pseudothrombocytopenia" by some authors, because it is related to platelet agglutination in vitro, rather than in vivo agglutination and clearance.

DDAVP should be administered IV every 8 hours, for 2-3 doses, and then q 48 hours. Standard dosing of desmopressin is 0.3 mcg/kg given over 30 min, with peak increments of FVIII and VWF 30–90 min after the infusion. NSAIDS should be used with caution with DDAVP, since they can aggravate hyponatremia. Tachyphylaxis and hypotension can occur with repeated doses. There have been reports of myocardial infarction after treatment with desmopressin. Desmopressin should be avoided in patients who are at very high risk for cardiovascular or cerebrovascular disease, especially the elderly.

If bleeding is not controlled with DDAVP, replacement VW concentrates should be used for types 1 and 2 disease at doses (based on VW factor units) of 20-30 units/kg 12 hours for 3-10 days. Factor VIII recombinant and Monoclonal products do not contain VWF. Cryoprecipitate on the other hand contains high levels of VWF,

For major bleeding and for Type III disease doses should be increased to 50 IU /kg. **Humate-P (CSL Behring)**, Alphanate SD/HT (Grifols USA, Los Angeles, CA, USA) and Wilate (Octapharma) are plasma-derived concentrates licensed in the United States to replace VWF in persons who have VWD. Humate is the factor concentrate available on formulary at UCLA. It is a pasteurized product with half life about 11.3 hours. It contains 2.5 U of RCo per 1 unit of FVIII, with efficacy of >90%<sup>6</sup>. Alphanate is pasteurized and contains 1.2U of RCo per 1 U of FVIII. It has efficacy between 75% and 95%<sup>7</sup>. Wilate is a high purity concentrate with a double virus inactivation, with

1U of RCo per 1U of FVIII. Efficacy is similar to the other two products<sup>8</sup>. All these products are manufactured at US-licensed facilities from pooled plasma collected from paid donors.

Antifibrinolytic agents such as aminocaproic acide (AMICAR<sup>®</sup>) may be useful for dental procedures. They inhibit the conversion of plasminogen to plasmin, inhibiting fibrinolysis and thereby helping to stabilize clots that have formed. Epsilon aminocaproic acid comes as elixir, tablets and in IV formulation. The dose is 100 mg/kg, followed by 50 mg/kg q 6 hours. Maximum dose is 18 gm/day. Tranexamic Acid-Cyclokapron and Lysteda (6-10 more potent than Amicar), comes in tablets and IV formulation. It is dosed at 25 mg/kg every 6-8 hours. Both IV formulations can be used effectively as a topical mouthwash. Both drugs should be avoided in the management of urinary tract bleeding.

It is critical to make a correct diagnosis of Von Willebrand Disease, since it has clinical and therapeutic implications. Knowledge of the genetics and biology of Von Willebrand Factor has improved treatment of Von Willebrand's Disease. Treatment of most surgical episodes in patients with VWD should be done with VWF concentrates. Surgeries should be done in centers with access to VWF:RCo and FVIII levels

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Submitted on November 24, 2013