

CASE REPORT

Von Willebrand Disease: The Intersection of Clinical and Laboratory Medicine

Menaka Pai, MD, FRCPC

Mark A. Crowther, MD, MSc, FRCPC

CASE PRESENTATION

A 16-year-old woman was referred for evaluation to the Outpatient Hematology Clinic as a result of a marginally prolonged partial thromboplastin time (PTT) found on routine screening prior to tonsillectomy. The PTT was 36 seconds (upper limit of normal: 35 seconds). The patient did not have a history of abnormal bleeding and described no history of bruising. She did not describe menorrhagia. She had not had prior surgery. She had not had hemorrhage at the time of dental surgery or with tooth loss. The remainder of the history and physical examination were unremarkable. Her father described his own medical history of massive hemorrhage (requiring multi-unit transfusion) at the time of his tonsillectomy 30 years prior. He had had three sinus surgeries all complicated by excess bleeding. Despite discussing his personal and family history of hemorrhage with the oral surgeon who performed his sinus surgery, no investigations had been performed on the father. A paternal uncle was also said to have had a near-fatal hemorrhage at the time of tonsillectomy.

On repeat testing, the woman had persistent prolongation of the PTT (39 seconds). The von Willebrand antigen (Ag) and ristocetin cofactor (RCoF) activity were markedly reduced (approximately 35%) and the factor VIII:C level was 55% (upper limit of normal: 50%). The von Willebrand multimer pattern was described as normal. After a 20 μ g desmopressin acetate (DDAVP) challenge, the factor VIII:C level, von Willebrand antigen and ristocetin cofactor activity were all greater than 150%. The father's laboratory examination revealed similar findings: baseline testing was consistent with type 1 von Willebrand disease.

VON WILLEBRAND DISEASE (vWD)

Von Willebrand disease is an uncommon hereditary bleeding disorder. The prevalence, based on referral for bleeding symptoms, is approximately 30 to 100 cases per million.¹ This is the same as the prevalence of hemophilia A. However, screening studies have identified that up to 1 to 2% of the

general population has quantitative or qualitative laboratory abnormalities of von Willebrand factor (vWF).¹ Therefore, von Willebrand disease is best understood as a *clinicopathologic diagnosis* – the finding of laboratory abnormalities of vWF in individuals with abnormal bleeding symptoms.

Von Willebrand factor is a large multimeric glycoprotein that is synthesized in vascular endothelium cells and megakaryocytes. It plays two key roles. vWF acts as a carrier protein for coagulation factor VIII (fVIII), protecting it from degradation by proteolytic enzymes.² vWF also binds glycoproteins on the surface of platelets, localizing them to sites of vascular endothelial injury and assisting in the formation of a “platelet plug.”³ In this way, vWF is essential to both primary (platelet-mediated) and secondary (coagulation factor-mediated) hemostasis.

DIAGNOSIS

Von Willebrand disease is a result of quantitative and/or qualitative abnormalities of vWF. It is classified into three groups: type 1 (mild-to-moderate quantitative deficiencies of vWF and fVIII), type 2 (qualitative abnormalities of vWF) and type 3 (severe quantitative deficiencies of vWF and fVIII). To differentiate between these subtypes, several laboratory tests must be performed.⁴

One must test the quantity of vWF via the vWF:Ag test, an enzyme-linked immunosorbent assay. The quality of vWF can be tested using the vWF:RCoF, vWF multimer and ristocetin-induced platelet aggregation (RIPA) tests. The vWF:RCoF uses ristocetin, an antibiotic that causes platelets to agglutinate in the presence of qualitatively normal vWF. Patients with type 2A, 2B and 2M vWD have a vWF:RCoF level that is disproportionately low, when compared with the vWF:Ag level. vWF multimers can be examined using gel electrophoresis. Patients with type 2A and 2B vWD have absent high molecular weight multimers on the gel. The RIPA test mixes low-dose ristocetin with the patient's platelet-rich plasma, which contains both vWF and platelets.

Samples from patients with type 2B vWD have increased aggregation with low-dose ristocetin, because their vWF binds more avidly to platelets. Other types of vWD have normal to decreased platelet aggregation on the RIPA test. It is important to understand that all of these tests have limited sensitivity, specificity and reproducibility. It is known that vWF levels are very sensitive to hormone levels, stress, pain, ABO blood group and a host of other factors.⁵ Because of the variability of vWF levels, a single normal value does not exclude von Willebrand disease. A single abnormal value should also be confirmed on repeat testing. The major subtypes of vWD are summarized in Table 1. The genetic characterization of vWD is a fast-moving area of research. To date, over 250 mutations have been identified.⁵

Individuals with von Willebrand disease are a clinically heterogeneous group. Their risk of bleeding depends on the quality and quantity of their vWF as well as the “bleeding challenges” they experience during their lifetime. It is essential to take a thorough clinical history, including questions about epistaxis, gum bleeding, excessive bruising, excessive bleeding from trivial wounds, surgical/dental bleeding, menstrual bleeding and anemia.⁶ Because vWD is an inherited disorder with variable penetrance, a detailed family history is also necessary.

MANAGEMENT

Depending on their phenotype, patients with vWD may not require any regular treatment. However they are at an increased risk for bleeding during “challenges.” For women with heavy menstrual bleeding, the combined oral contraceptive pill and antifibrinolytic agents (e.g., tranexamic acid) are effective in reducing bleeding. Patients with vWD often need prophylaxis around the time of surgical procedure. For patients with type 1 vWD, intranasal, subcuta-

neous or intravenous DDAVP can increase circulating vWD levels by encouraging its release from endothelial cell stores. Patients with type 2 vWD, who have qualitatively abnormal vWF, or type 3 vWD, who have little to no stored vWF, rarely benefit from DDAVP. They can be treated with Humate-P®, a human-derived medium purity factor VIII concentrate complexed to vWF.⁵

Though von Willebrand disease is a rare entity, it has significant clinical consequences and effective treatment options. Physicians can make the diagnosis of von Willebrand disease by combining information from the laboratory with a detailed personal and family history.

Key Points for Diagnosis and Management of von Willebrand disease

- Von Willebrand disease (vWD) is an uncommon hereditary bleeding disorder, caused by quantitative or qualitative defects in von Willebrand factor (vWF)
- If you suspect vWD, take a detailed family history and ask patients about their response to “bleeding challenges:”
 - Epistaxis
 - Gum bleeding
 - Excessive bruising
 - Excessive bleeding from trivial wounds
 - Surgical/dental bleeding
 - Menstrual bleeding
- Patients with mild (type 1) vWD may not require any treatment
- During bleeding challenges, several agents can be used for prophylaxis and treatment:
 - Combined oral contraceptive pill for menorrhagia
 - Antifibrinolytic agents (e.g., tranexamic acid)
 - Intranasal, subcutaneous or intravenous desmopressin acetate (DDAVP)
 - Humate-P®, a human derived medium purity factor VIII concentrate complexed to vWF

Table 1. Subtypes of von Willebrand Disease⁴

	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3
Essential problem	Mild quantitative deficiency	Decreased platelet binding	Increased platelet binding	Decreased platelet binding	Decreased fVIII binding	Severe quantitative deficiency
vWF:Ag	Low	Normal to low	Normal to low	Normal to low	Normal	Low to absent
vWF:RCoF	Low	Low	Low	Low	Normal	Low
fVIII	Normal to low	Normal to low	Normal to low	Normal to low	Low	Low
RIPA	Normal	Low	High	Low	Normal	Low
PTT	High	High	High	High	High	High
Platelets	Normal	Normal	Low	Normal	Normal	Normal
Multimers	Normal weight forms absent	High molecular weight forms absent	High molecular	Normal	Normal	All forms absent
Inheritance pattern	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive	Autosomal recessive
% of patients with vWD	60 to 80%	10 to 30%	10 to 30%	10 to 30%	10 to 30%	1 to 5%

Abbreviations: Ag=antigen; fVIII=factor VIII; PTT=partial thromboplastin time; RCoF=ristocetin cofactor; RIPA= ristocetin-induced platelet aggregation; vWD= von Willebrand disease; vWF= von Willebrand factor

CASE REVISITED

The 16-year-old patient ultimately underwent successful tonsillectomy after receiving 20 μg of DDAVP intravenously. With this treatment the estimated blood loss for the surgery was minimal. †

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Author Biographies

Dr. Menaka Pai is a hemostasis and thrombosis fellow at McMaster University. She is enrolled in the Clinician Investigator Program and is completing her Master's degree in the Health Research Methodology Program. Dr. Pai's research interests include the development of standardized clinical assessment tools for mild bleeding disorders and knowledge translation strategies to encourage appropriate venous thromboembolism prophylaxis.

Dr. Mark Crowther is a professor and director of the Division of Hematology and Thromboembolism at McMaster University. His clinical interests include benign hematology with a special focus on the prevention and treatment of blood clotting complications. Dr. Crowther holds a Career Investigator Award from the Heart and Stroke Foundation of Canada. His current research interests include improving the use of current anticoagulant drugs, the use of vitamin K to treat warfarin-associated coagulopathy, and the use of low molecular weight heparin in patients with renal failure.