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VON WILLEBRAND DISEASE: AN INTRODUCTION FOR THE PRIMARY CARE PHYSICIAN

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David Lillicrap and Paula James

Introduction

von Willebrand disease (VWD) is the most common type of bleeding disorder, affecting up to 1% of the world's population. Since symptoms are often mild, a significant majority of patients remain undiagnosed. With all forms of VWD, however, bleeding episodes can be severe and may require treatment, particularly during or following surgery or dental work.

The diagnosis of VWD is complex and should be made by physicians experienced in the treatment of bleeding disorders. However, the primary care physician can and should play a role in recognizing the signs and symptoms of VWD and in referring patients for proper management.

History of VWD

In 1926, Dr. Erik von Willebrand, a Finnish physician, published the first manuscript describing an inherited bleeding disorder with features that suggested it was distinct from hemophilia [1]. This disorder is now known by the name of its discoverer.

Dr. von Willebrand's studies began with an assessment of a family living on the island of Föglö in the Äaland archipelago in the Baltic Sea. The propositus in this family bled to death in her teens from menstrual bleeding, and four other family members had also died as a result of uncontrolled bleeding. In these initial studies, Dr. von Willebrand noted that the patients had a prolonged bleeding time despite having a normal platelet count, and exhibited an autosomal dominant mode of transmission of the bleeding problem.

During the 1950s and early 1960s, it became apparent that this condition was also usually associated with a reduced level of factor VIII (FVIII) activity, and that this deficiency could be replaced through the infusion of plasma or plasma fractions. In 1971 a significant advance was made by two groups of investigators who showed, for the first time using immunologic assays, that FVIII and von Willebrand factor (VWF) were distinct proteins. This finding was also accompanied by a new laboratory strategy to evaluate platelet function in this condition.

The distinct nature of VWF was definitively demonstrated by the characterization of the VWF gene in 1985 by four independent groups of investigators. This discovery has subsequently led to an improved understanding of the genetic basis of VWD and the potential for developing new therapeutic approaches to the condition.

What is VWD?

VWD is the most common inherited bleeding disorder in humans. The central feature of all forms of VWD is the presence of reduced amounts of VWF or abnormal forms of VWF in the circulation.

Epidemiology

VWD shows a worldwide distribution, and is also common in other animal species including dogs and pigs. Its prevalence in the human population varies depending upon the approach undertaken to define the diagnosis. In two large prospective epidemiologic studies, up to 1% of a predominantly pediatric population has been found to manifest symptoms and laboratory signs of VWD [2, 3]. In contrast, the prevalence of the most severe form of the disease (type 3 VWD) has been estimated in several different countries to be between 1 and 3 per million [4].

The prevalence of VWD presenting with bleeding symptoms to primary care physicians appears to be approximately 1 in 1,000. In all studies of VWD, the prevalence in women is approximately twice that documented in men, presumably because of the unique potential of menorrhagia in females.

VWF genetics

VWF is encoded by a gene on human chromosome 12. Thus, the VWF status of every individual represents the combined output from maternally and paternally inherited VWF gene copies. The gene is very large (178 kb) and complex (52 exons), making molecular genetic analysis complicated.

The VWF protein

VWF is synthesized in two cell types, vascular endothelium and megakaryocytes. The secreted VWF protein comprises a repeated 2,050 amino acid subunit that is processed into large polymers (multimers) of the protein. Each of these subunits contains binding sites for collagen (in the subendothelial matrix), FVIII, and platelets (the GPIb and GPIIb/IIIa receptors). Normal regulation of VWF multimer size and the preservation of the various binding sites on the VWF subunit are essential for the physiological function of VWF.

Following synthesis, VWF is either secreted into the plasma or subendothelium, or stored in cytoplasmic organelles in the endothelium (Weibel-Palade bodies) and platelets (alpha granules). VWF can be released from these stores in response to a variety of physiological and pharmacological stimuli.

Biological functions of VWF

In contrast to most of the other coagulation factors, VWF functions in hemostasis as an adhesive protein that binds to several ligands that are critical components of the hemostatic process (Figure 1).

VWF binds to:

1. Platelets and the subendothelium to promote platelet adhesion.
2. Activated platelets to promote platelet aggregation.
3. FVIII to prevent premature degradation of this coagulation cofactor.

Figure 1

The role of von Willebrand factor in hemostasis

- Mediates platelet adhesion to the damaged vessel wall
- Participates in platelet aggregation
- Carrier protein for factor VIII

Types of VWD

The International Society on Thrombosis and Haemostasis last published their official recommendations concerning VWD classification in 2006 [5]. In this classification, VWD is considered as either a quantitative (type 1 and type 3) or qualitative (type 2) trait (Figure 2).

Type 1 VWD

This is the most common form of VWD, accounting for ~80% of all cases. The condition is transmitted as an autosomal dominant trait with incomplete penetrance. Type 1 disease is characterized by a mild to moderate (0.05-0.50 U/mL) reduction in plasma levels of VWF. The VWF is functionally normal and the plasma level of factor VIII coagulant activity (FVIII:C) is reduced in proportion to the VWF level. Patients manifest a spectrum of mucocutaneous bleeding symptoms, the severity of which usually correlates with the level of their VWF deficiency.

Type 3 VWD

Type 3 disease has a prevalence of between 1 and 3 per million in most populations, although in certain locations where consanguineous marriages are more frequent the prevalence is significantly higher. The condition is inherited as an autosomal recessive trait, with most parents of type 3 patients showing few if any symptoms of bleeding. In type 3 disease, VWF levels are always less than 0.05 U/mL and are often undetectable. The plasma FVIII:C level is reduced to between 0.01 and 0.10 U/mL. These patients manifest severe recurrent mucocutaneous bleeding, as well as frequent soft tissue and musculoskeletal bleeding. Over time, if treatment is inadequate, chronic musculoskeletal damage occurs and type 3 patients may require joint replacement surgery in middle age.

Type 2 VWD

The current classification of VWD recognizes four distinct qualitative forms of VWD: types 2A, 2B, 2M, and 2N disease. The clinical manifestations of the type 2 variants of VWD are similar to those of type 1 disease.

Type 2A VWD

This condition represents a loss of the platelet-dependent function of VWF through the absence of the high molecular weight forms of the protein.

Type 2B VWD

This VWD subtype represents a classical gain-of-function genetic trait. Type 2B VWD mutations enhance the binding of VWF to the glycoprotein Ib platelet receptor and result in spontaneous VWF-platelet interactions in the circulation, a phenomenon that does not occur with normal VWF. As a result of the abnormal platelet interactions, these patients often show mild/moderate thrombocytopenia (low platelet count).

Type 2M VWD
This VWD subtype represents the loss-of-function equivalent of type 2B disease.

Type 2N VWD
Type 2N VWD is inherited as an autosomal recessive trait caused by mutations in the FVIII binding site.

Figure 2

Classification of von Willebrand disease

International Society on Thrombosis and Haemostasis guidelines 2006 [5]:

Type 1 Mild/moderate deficiency of qualitatively normal VWF

Type 2 Qualitative mutants

Type 2A: reduced platelet-dependent function with abnormal multimers

Type 2B: increased affinity for platelet binding

Type 2M: reduced platelelet-dependent function with normal multimers

Type 2N: reduced FVIII binding

Type 3 Severe deficiency of VWF

Diagnosis of VWD

The diagnosis of VWD requires attention to three clinical and laboratory components (Figure 3): a personal history of excessive mucocutaneous bleeding, a family history of excessive bleeding, and a laboratory evaluation that is consistent with a quantitative and/or qualitative defect in VWF.

Figure 3

Diagnostic criteria for von Willebrand disease

1. Personal history of excessive mucocutaneous bleeding
2. Laboratory tests of hemostasis consistent with VWD
3. Family history of excessive bleeding

Symptoms of VWD

The clinical assessment of VWD relies heavily upon the acquisition of an objective personal history of excessive mucocutaneous bleeding (Figure 4). Many of the bleeding symptoms seen in VWD also occur frequently in the normal population. Thus, while a standard clinical history may identify patients with an excessive bleeding tendency, relatively brief and validated bleeding scoring questionnaires are now available and may facilitate the identification and classification of "clinical bleeders" [6, 7].

The most frequent symptoms experienced by patients with VWD are:
- recurrent epistaxes
- prolonged bleeding from lacerations
- easy bruising
- gingival bleeding
- menorrhagia
- prolonged post-procedural bleeding
- heavy or prolonged bleeding after childbirth

Figure 4

Diagnostic symptoms of von Willebrand disease

- Easy bruising
- Prolonged bleeding from lacerations
- Epistaxes
- Bleeding from gums
- Menorrhagia
- Post-dental procedural bleeding
- Post-surgical bleeding
- Excessive post-partum bleeding
- Muscle hematomas (type 3 VWD)
- Hemarthroses (type 3 VWD)

In some women with VWD, menorrhagia may be the only bleeding manifestation. It is therefore especially important to conduct a detailed assessment of the patient's menstrual history [8].

Prolonged and excessive bleeding is often documented after oral surgical procedures such as tonsillectomy and wisdom teeth extraction. In contrast, soft tissue bleeds, muscle hematomas, and hemarthroses are rarely encountered in VWD, except in the severe type 3 form of the disease, where very low FVIII levels accompany undetectable levels of VWF.

Because the bleeding tendency in VWD is relatively mild in many patients and will only pose problems with provocation of hemostasis (i.e. with surgery or trauma) there may not be an obvious clinical history of spontaneous bleeding problems. This may be especially true in young children and males in who challenges to the hemostatic system may not have been encountered.

In patients with the severe form of VWD (type 3), symptoms typical of hemophilia, such as hemarthrosis and muscle hematomas, are the result of concomitantly reduced FVIII levels.

Family history

Most cases of VWD are inherited, and thus there is often evidence of a family history of excessive bleeding (Figure 5). However, this issue is complicated by the fact that some forms of the disease show incomplete penetrance of the bleeding symptoms. In most cases, the disease is inherited as a dominant trait. In contrast, the severe type 3 form of the disease shows a recessive pattern of inheritance, with parents who do not usually manifest clinical symptoms.

Figure 5

Inheritance patterns of von Willebrand disease

Type 1 VWD	Autosomal dominant ~70% penetrance
Type 2 VWD	2A, 2B, and 2M - Autosomal dominant 2N - Autosomal recessive
Type 3 VWD	Autosomal recessive

Primary care physicians who see patients with a history consistent with VWD should:

- Refer the patient to a centre with physicians experienced in the management of bleeding disorders.
- Avoid initiating testing for VWD in laboratories that are not experienced in evaluating VWF and FVIII levels and function.

Laboratory testing

In the hemostasis laboratory, the critical components of VWD diagnosis involve quantitative and qualitative measurements of VWF and FVIII (Figure 6).

Figure 6

Laboratory tests for VWD

Test	Purpose
Factor VIII coagulant activity (FVIII:C)	Measures the functional activity of factor VIII
von Willebrand factor antigen (VWF:Ag)	Measures the amount of VWF
Ristocetin co-factor and/or collagen binding activity (VWF:RCo and/or VWF:CB)	Measures the functional activity of VWF
von Willebrand factor multimers	Provides a visualization of how well the VWF monomer is multimerized (joined into chains)
Ristocetin induced platelet aggregation (RIPA)	Measures how sensitive VWF is to ristocetin (useful in diagnosing Type 2B VWD)

Primary care physicians should know the following facts about laboratory testing for VWD:

- Both VWF and FVIII are acute phase proteins and thus their plasma levels can vary significantly with a number of environmental variables including stress, exercise, the phase of the menstrual cycle, hormone treatment, and pregnancy.
- Genetic factors, including the ABO blood group, can significantly affect the plasma levels of VWF and FVIII.
- Inter-laboratory standardization of some of the tests for VWD (i.e. VWF:RCo and the VWF multimer test) has proved to be challenging.

Interpretation of the laboratory results involved in making the diagnosis of VWD is often very difficult (Figure 7). To avoid misdiagnosis, it is strongly advised that physicians experienced in the clinical care of VWD perform this component of the diagnostic algorithm.

The role of the platelet function analyser, the PFA-100®, in VWD diagnosis remains unresolved. Generally speaking, the bleeding time should not be used as a screening test for VWD. There may, however, be geographical exceptions to this recommendation. Thus, where specific tests for VWF are not available

Figure 7

Common laboratory findings associated with various types of VWD

	Type 1	Type 3	Type 2A	Type 2B	Type 2M	Type 2N
VWF: Ag	↓ or ↓↓	absent (<0.05 U/mL)	↓	↓	↓	normal or ↓
VWF: RCo	↓ or ↓↓	absent (<0.05 U/mL)	↓↓ or ↓↓↓	↓↓	↓↓	normal or ↓
FVIII:C	normal or ↓	0.01-0.10 U/mL	normal or ↓	normal or ↓	normal or ↓	↓↓ or ↓↓↓
VWF:RCo / VWF:Ag ratio	>0.6	not useful	<0.6	<0.6	<0.6	>0.6
Multimers	normal	absent	loss of high (and possibly intermediate) molecular weight multimers	loss of high molecular weight multimers	normal	normal

↓: slightly reduced ↓↓: moderately reduced ↓↓↓: severely reduced

(i.e. in some regions of developing countries), a low FVIII with a prolonged bleeding time may help identify patients with type 3 VWD.

In addition to abnormalities of hemostasis, patients with VWD, and in particular women with menorrhagia, may also have manifestations of chronic blood loss with an iron deficiency anemia, or iron deficiency alone without anemia.

Prevention and Treatment of Bleeding

In general terms, the treatment of VWD can be divided into two types: adjunctive therapies that aim to provide an indirect hemostatic benefit, and treatments that increase the plasma levels of VWF and FVIII [9].

Adjunctive therapies

A number of adjunctive therapies can be used with significant benefit in VWD, particularly in circumstances such as at the time of minor surgical and dental procedures, and to treat menorrhagia (Figure 8). These interventions include the use of antifibrinolytic agents such as tranexamic acid and epsilon aminocaproic acid and the application of topical hemostatic preparations such as fibrin glue to exposed sites of bleeding. In women with menorrhagia, the administration of hormonal therapy in the form of combined contraceptives (that work, at least in part, by their estrogen component elevating VWF and FVIII levels) or progesterone containing intrauterine systems (such as Mirena®) often results in a significant clinical benefit. Additionally, replacement of iron stores in individuals with iron deficiency can result in an improved quality of life.

Figure 8

Adjunctive therapies for von Willebrand disease

Antifibrinolytic agents	Tranexamic Acid Epsilon aminocaproic acid
Fibrin glue	
Estrogens	

Factor-boosting therapies

To increase VWF and FVIII levels acutely in VWD patients, two approaches have been extensively utilized: parenteral or nasal administration of desmopressin, and the intravenous infusion of plasma-derived VWF/FVIII concentrates (Figure 8).

Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) is a synthetic analogue of the antidiuretic hormone vasopressin. We now have more than 25 years of clinical experience with desmopressin in treating VWD, and intravenous, subcutaneous, and intranasal routes of administration have all been extensively utilized [10]. It is important to note that the hemostatic dose of DDAVP is higher than the dose used for the control of enuresis.

The side effects of desmopressin have been well characterized and, in the vast majority of cases, they are transient and minor in nature. Mild tachycardia, headache, and facial flushing are not infrequent, and because some patients feel lightheaded following administration, the agent is best given with the patient sitting or lying down. Due to its mild antidiuretic effect, fluid intake should be limited to replacement volumes only in the 24 hours following administration. Fortunately, episodes of fluid overload and severe hyponatremia (that can result in seizures) are rare, and most often involve the very young or post-partum patients. Desmopressin has been used successfully and safely to prevent bleeding in early pregnancy.

Desmopressin has a role in preventing or treating bleeding episodes in some patients with type 1, 2A, 2M, and 2N VWD. Desmopressin is not effective in type 3 patients, and may exacerbate the thrombocytopenia that is often seen in patients with type 2B VWD.

The peak hemostatic effect of the standard dose of desmopressin (0.3 µg/kg) occurs between 0.5 and 1 hour following administration, with an average VWF/FVIII increment of 3- to 5-fold over baseline values. However, given the relatively unpredictable nature of the desmopressin response, all VWD patients should undergo a therapeutic trial of administration to assess their individual level of response. If an initial, adequate hemostatic benefit is documented (>3-fold increment of VWF:RCo and VWF:Ag to levels of >0.30 U/mL), this treatment approach can be used for the prevention of bleeding associated with minor surgeries and dental procedures, and to treat severe menstrual bleeding. If repeated administration of desmopressin is required, this should not occur more often than daily, and, even then, subsequent treatments are likely to result in reduced responses (~70% of the initial VWF and FVIII increments).

VWF/FVIII Concentrate

In those VWD patients in whom desmopressin is either ineffective or contraindicated, or in instances where it is anticipated that the risk of major bleeding is high or where the duration of hemostatic support required is longer than 2-3 days, VWF and FVIII levels can be restored by the infusion of plasma-derived concentrates of these proteins. The inability to virally inactivate cryoprecipitate (the previous blood product of choice for VWD), and the lack of any licensed recombinant VWF concentrate has resulted in the extensive use of several plasma-derived VWF/FVIII products.

Figure 9

Strategies for increasing von Willebrand factor levels

1. Release of intrinsic VWF stores
   Desmopressin (DDAVP) - IV, SC, IN
2. Administration of VWF concentrate
   Plasma-derived VWF/FVIII concentrates

IV: intravenous
SC: subcutaneous
IN: intranasal

Pregnancy and VWD

Pregnancy in women with VWD poses a special clinical challenge that merits brief discussion. As VWF is an acute phase reactant, synthesis of the protein increases throughout pregnancy to reach levels >3.0 U/mL at term in a normal woman. While levels do not increase as much as in normal subjects, in type 1 VWD the levels of the protein will often rise to within the normal range. To ensure optimal peripartum management, VWF and FVIII levels should be measured in the third trimester to prepare for possible epidural anesthesia and a safe delivery. Following delivery, VWF levels fall quickly, and all women with VWD must be cautioned about the potential of developing a significant secondary post-partum hemorrhage between 5-14 days after delivery.

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