THE BASIC SCIENCE, DIAGNOSIS, AND CLINICAL MANAGEMENT OF VON WILLEBRAND DISEASE

Second Edition

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The Basic Science, Diagnosis, and Clinical Management of von Willebrand Disease

David Lillicrap

Historical Perspective of von Willebrand Disease

In 1926, Dr. Erik von Willebrand, a Finnish physician, published the first manuscript describing an inherited bleeding disorder with features that suggested that this 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 Åland 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 before her 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 procoagulant activity (FVIII:C), 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 factor VIII (FVIII) and von Willebrand factor (VWF) were distinct proteins. This finding was also accompanied by a new laboratory strategy employing ristocetin 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 von Willebrand disease (VWD) and the potential for developing new therapeutic approaches to the condition.

Basic Science of von Willebrand Disease

The central feature of all forms of VWD is the presence of reduced amounts of VWF or abnormal forms of VWF in the circulation.

von Willebrand factor gene
VWF is encoded by a gene on the short arm of human chromosome 12. The gene spans 178 kilobases (kb) of DNA and comprises 52 exons that encode a mRNA of ~9 kb. In addition to its large size and genomic complexity, analysis of the VWF gene is further complicated by the presence on chromosome 22 of a partial pseudogene copy of exons 23 to 34 of the chromosome 12 sequence. This non-functional evolutionary remnant shows a 3% sequence divergence from the chromosome 12 gene, and appears to have been generated at about the time that the higher order primates diverged from monkeys.

The VWF gene is expressed exclusively in two cell types: vascular endothelium and megakaryocytes. Transcription of the gene is regulated by a combination of ubiquitous and cell type-specific transcription factors, including GATA and ETS proteins. There are also several transcriptional repressive elements in the upstream sequence of the gene.

von Willebrand factor protein
The nascent VWF protein comprises 2,813 amino acids (AA) that, through a series of complex post-translational events, are modified to produce a 2,050 AA mature VWF subunit (molecular weight ~260 kDa) that is secreted from the cell of synthesis (Figure 1). Critical to this biosynthetic process is the removal of pre- and pro-peptide domains of the precursor protein, N- and O-linked glycosylation, and the development of polymers (multimers) of the mature VWF subunit. This latter event is initially achieved through inter-subunit
disulphide bond formation at the carboxyl termini of the protein to form VWF dimers, and subsequently through further inter-subunit disulphide linkages at the N-terminus to generate VWF multimers that can reach molecular weights of ~20 million Daltons.

The primary structure of the VWF protein is comprised of several repeated domains designated A through D (Figure 2). The D1, D2, D’, and D3 domains are involved in regulating the process of multimer formation, and the D’ and D3 regions also mediate FVIII binding. The A1 and A3 domains both possess collagen-binding properties. The sites of VWF binding to platelets are through the A1 domain to the platelet glycoprotein Ib/IX receptor (GpIb/IX), and the C2 domain to the glycoprotein IIb/IIIa (GpIIb/IIIa) receptor. Thus, each VWF monomer possesses domains that enable the protein to bind to ligands on platelets (GpIb/IX and GpIIb/IIIa), in the subendothelium (collagen) and in the circulation (FVIII).

Following synthesis, VWF is secreted via one of two distinct pathways: a persistent, constitutive release pathway or, following regulated release from sites of intracellular storage. In the megakaryocyte (and platelet) the fully multimerized VWF is stored in alpha granules, while in endothelial cells the protein is diverted to the rod-shaped Weibel-Palade bodies in the cytosol. VWF shares these storage sites with several other proteins, which are released in response to a variety of physiological and pharmacological stimuli, including thrombin, shear stress, and desmopressin.

After release from its cell of synthesis, recent information suggests that ultra-large VWF
multimers bind to the surface of the endothelial cell, at least in part, through an interaction with the Weibel-Palade membrane protein, P-selectin. In this location, the VWF multimers are subjected to shear stresses from flowing blood, and a physiological reduction in the size of the multimers occurs through a controlled proteolytic cleavage event. The cleavage site on VWF is in the A2 domain between AAs 1605 and 1606, and the cleavage is mediated by the metalloproteinase, ADAMTS13 [2, 3].

Biological functions of von Willebrand factor
The structure of VWF suggests that its major functional role involves binding to several ligands in the circulation and the damaged vessel wall (Figure 3). Thus, it is of no surprise that the protein’s three physiological functions are: to mediate platelet adhesion to sites of vascular injury through binding platelet GpIb/IX and collagen in the vascular subendothelium; to facilitate platelet aggregation through binding the platelet GpIIb/IIIa receptor; and to bind to and protect FVIII from proteolytic degradation by activated protein C in the circulation.

Clinical Features of von Willebrand Disease

Epidemiology of von Willebrand disease
VWD is the most common inherited bleeding disorder in humans. The disorder shows a worldwide distribution, and it 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 at least two large
Figure 3

The figure shows an area of endothelial cell loss with the sequence of events involved in the primary hemostatic event, platelet plug formation. The platelets initially adhere transiently to subendothelial VWF through the GpIb/IX receptor. This contact significantly slows the movement of the platelets that continue to roll across the subendothelium, maintaining an interaction with VWF and collagen through the GpIb/IX and platelet collagen receptor(s), respectively. Eventually these contacts reach a threshold that signals the event of platelet activation. The platelets then adhere stably to the damaged vessel wall, and undergo an aggregation response through a platelet GpIIb/IIIa receptor-mediated event.

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prospective epidemiologic studies, up to 1% of a predominantly pediatric population has been found to manifest symptoms, and laboratory signs, of VWD [4,5]. In contrast, the prevalence of severe, type 3 VWD has been estimated in several different countries to be between 1 and 3 per million, while the number of symptomatic cases of VWD referred to tertiary care medical centres, is approximately 10 to 30 per million population [6]. The prevalence of VWD presenting with bleeding symptoms to primary care physicians is now thought to be approximately 1 per 1,000.

Classification of von Willebrand Disease

The International Society on Thrombosis and Haemostasis last published their official recommendations concerning VWD classification in 2006 [7]. In this classification, VWD is considered as either a quantitative (type 1 and type 3) or qualitative (type 2) trait (Figure 4).

**Type 1 von Willebrand disease**

This is the most common form of VWD, accounting for approximately 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 (0.45-0.05 U/mL) reduction in VWF:Ag and VWF:RCo plasma levels. The VWF is functionally normal, as is the range of plasma VWF multimers; the plasma level of FVIII:C is reduced in proportion to the VWF level. These patients manifest a spectrum of mucocutaneous bleeding symptoms, the severity of which usually correlates with the level of their VWF deficiency. The initial molecular genetic studies of type 1 disease indicate that many cases appear to be due to missense mutations in the
VWF gene. There is also growing evidence to suggest that the cause of mild VWF reductions is likely to involve contributions from genes other than VWF and the ABO blood group genes. While there appear to be many different type 1 disease-causing mutations, at least one, a tyrosine to cysteine mutation at codon 1584, is found in 10-20% of patients in North America and Europe [8].

**Type 3 von Willebrand disease**

Type 3 VWD 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, the VWF:Ag and VWF:RCo levels are always <0.05 U/mL and are often undetectable. The plasma FVIII:C level is reduced to between 0.01-0.10 U/mL. Plasma multimers are usually absent, but may be detected after prolonged exposure of the test autoradiograph. 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 von Willebrand disease**

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

**Type 2A von Willebrand disease**

This condition represents a loss of the platelet-dependent function of VWF through the absence of the high molecular weight forms of the protein. There is either a biosynthetic inability to make these multimers, or they are made, secreted, and subsequently degraded.
The hallmark of type 2A disease is a low VWF:RCo to VWF:Ag ratio (<0.6), with absent high molecular weight VWF multimers and impaired RIPA. Missense mutations resulting in type 2A disease have been characterized in the D2, D3, A1, A2, and C terminal domains of VWF.

**Type 2B von Willebrand disease**

This VWD subtype represents a classical gain-of-function genetic trait. The condition is the result of a variety of dominant missense mutations in the GpIb binding region of the VWF A1 domain. These mutations enhance the binding of VWF for this platelet receptor and result in spontaneous VWF-platelet interactions in the circulation, a phenomenon that does not occur with normal VWF. On blood smears, this interaction can be seen as platelet clumping, and this same abnormality often results in mild chronic thrombocytopenia. In other testing, the VWF:RCo to VWF:Ag ratio will often be <0.6, and there is a deficit of the high molecular weight VWF multimers in the plasma, because they have bound to the platelets (Figure 5). A further critical test to confirm the presence of type 2B disease is the demonstration of enhanced RIPA using platelet-rich plasma from the patient, and ristocetin concentrations of <0.6 mg/mL.

This constellation of clinical and laboratory findings can also be seen in a rare inherited platelet disorder, platelet-type or pseudo-VWD. In this dominantly inherited trait, gain-of-function missense mutations are found in the platelet glycoprotein Ibα gene resulting in an increased affinity of binding to the VWF A1 domain. To differentiate between type 2B and
platelet-type VWD requires either testing for ristocetin-induced agglutination of washed patient platelets mixed with normal plasma (which will show enhanced reactivity in platelet-type but not type 2B VWD) or analysis of the VWF and GpIbα genes.

**Type 2M von Willebrand disease**
This VWD subtype represents the loss-of-function equivalent of type 2B disease. Most of the missense mutations resulting in type 2M VWD have again been localized to the A1 domain of VWF. In type 2M disease, the VWF:RCo to VWF:Ag ratio is also <0.6, but the features that are distinct from type 2B disease include the lack of platelet clumping (and thus thrombocytopenia), and the presence of a normal plasma multimer pattern.

**Type 2N von Willebrand disease**
This final qualitative mutant form of VWD is different from all other types in several respects. Its inheritance pattern is autosomal recessive and the only laboratory abnormality is often a reduced plasma FVIII level (usually between 0.10 and 0.40 U/mL). Type 2N VWD is one of the differential diagnosis for an isolated mild to moderately low FVIII level [9]. Other possibilities include mild hemophilia A or, in women, the carrier state for hemophilia A. The mutations responsible for this phenotype cluster in the region of the VWF gene encoding the D' FVIII binding domain (exons 18-25) and all affected individuals show one of three patterns of mutation: homozygosity for a FVIII binding missense mutation; compound heterozygosity for two different FVIII binding mutations; or the co-inheritance of a FVIII binding mutation and a VWF null mutation. Confirmation of type 2N VWD requires either direct demonstration of reduced FVIII binding or the documentation of an appropriate type 2N VWD genotype.

**Diagnosis of von Willebrand Disease**
The diagnosis of VWD requires attention to three clinical and laboratory components: 1) a personal history of excessive mucocutaneous bleeding, 2) a family history of excessive bleeding, and 3) a laboratory evaluation that is consistent with a quantitative and/or qualitative defect in VWF.

**Clinical assessment of von Willebrand disease**
The clinical assessment of VWD relies heavily upon the acquisition of an objective personal history of excessive mucocutaneous bleeding. Recurrent epistaxes, gingival bleeding, prolonged bleeding from lacerations, and easy bruising are all frequent in VWD. Given that the only manifestation of excessive bleeding in women with VWD may be menorrhagia, it is especially important that a detailed assessment of the patient’s menstrual history be undertaken [10]. 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 type 3 disease, where levels of FVIII are almost always <0.10 U/mL.

Because many of the bleeding symptoms seen in VWD also occur frequently in the normal population, the development of a formal bleeding questionnaire may prove to be an efficient and consistent means of identifying patients with increased bleeding, especially in a primary care setting. The value of such a detailed bleeding assessment in the tertiary referral setting is less clear [11].

**Family history in von Willebrand disease**
Most types of VWD are inherited as an autosomal dominant trait, and thus there may be evidence of a family history of excessive bleeding. However, this issue is significantly complicated by the fact that most forms of the disease show incomplete penetrance of the phenotype, and variable expressivity of bleeding symptoms within families [12]. In contrast, the severe type 3 form of the disease shows a recessive pattern of inheritance with parents that do not usually manifest clinical symptoms. Finally, type 2N VWD, in which isolated low FVIII levels occur, also shows a recessive pattern of inheritance, and thus, here again, a family history may be absent.

**Laboratory testing for von Willebrand disease**
In the hemostasis laboratory, the critical components of VWD diagnosis involve quantitative and qualitative measurements of VWF and FVIII [13].
If the patient has a chronic history of blood loss, there may be an accompanying iron deficiency anemia; mild chronic thrombocytopenia is often seen with type 2B VWD. The bleeding time should not be used as a routine screening test for VWD, and the exact role of the platelet function analyser, the PFA100®, in VWD diagnosis remains unresolved. Aside from these screening laboratory tests, the most useful investigations for diagnosis are: an immunological assay for VWF protein, the VWF antigen assay (VWF:Ag), a functional test for VWF, the ristocetin cofactor assay (VWF:RCo), and a test for FVIII pro-coagulant function (FVIII:C). Local normal ranges for these assays should be established, and due to the significant temporal variability of the VWF and FVIII values, testing must be repeated at least twice before a diagnosis of VWD is established.

The effect of the ABO blood group on VWF and FVIII levels is now well recognized, with blood group “O” individuals having levels 20-25% lower than those seen in “non-O” individuals [14]. This observation does not, however, necessitate a comparison against an ABO-matched plasma standard.

Finally, a number of “environmental” and acquired factors need to be considered when evaluating these studies. The effect of estrogens on elevating VWF and FVIII levels must be kept in mind during pregnancy and in patients on an oral contraceptive. Low VWF/FVIII levels can be seen in association with hypothyroidism. Other conditions in which VWD is acquired through the generation of auto-antibodies to VWF include a variety of lymphoproliferative and myeloproliferative diseases, and monoclonal gammopathies of undetermined significance.

Where VWF and FVIII studies show a reduction below the local normal range, further studies need to be considered to subtype the disease. Approximately 80% of patients will have type 1 disease in which a mild to moderate quantitative reduction in normal VWF is present (VWF levels between 0.05 and 0.5 U/mL; normal range 0.5-2.0 U/mL).

When the VWF:RCo to VWF:Ag ratio is consistently <0.6, the potential for a type 2 form of the disease is significant, and an analysis of the VWF multimer profile should be performed. Ristocetin-induced platelet agglutination (RIPA) must be carried out to define the presence of types 2A, 2B or 2M disease (Figure 4). The collagen binding assay has also been used to characterize type 2 VWD variants. Where an isolated low FVIII level suggests the presence of type 2N disease, FVIII binding studies and/or VWF genotyping should be performed.

The current role of molecular genetic testing in the diagnosis of VWD remains limited. Aside from confirming a diagnosis of type 2N disease through the identification of mutations in exons 18-24, and perhaps consolidating a diagnosis of type 2B or 2M disease through a study of exon 28 sequences, this testing format is not of routine diagnostic benefit. Initial studies of the molecular genetic basis of type 1 VWD have shown that many different VWF missense substitutions and other types of mutation may result in this phenotype [15-17]. In addition, approximately 40% of patients have no obvious mutations in the promoter, coding regions, and splice sites of the VWF gene, and thus may have mutations involving other genes influencing VWF biosynthesis or clearance. In summary, it is not clear whether any molecular genetic strategy would improve the currently available diagnostic testing for type 1 disease.

**von Willebrand Disease During Pregnancy**

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 and allow for the safe administration of an epidural anesthetic and a normal delivery. Interestingly, the increased synthesis of the gain-of-function mutant protein (type 2B disease) further exacerbates the platelet reactivity and the thrombocytopenia progressively worsens up to term. 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 and 14 days after delivery.
Prevention and Treatment of Bleeding in von Willebrand Disease

In general terms, the treatment of VWD can be divided into two types: a number of adjunctive therapies that aim to provide an indirect hemostatic benefit, and several treatments that increase the plasma levels of VWF and FVIII (Figure 6) [18, 19].

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. These interventions include the use of antifibrinolytic agents such as tranexamic acid and epsilon amino-caproic acid, and the application of topical hemostatic preparations, such as fibrin glue, to exposed sites of bleeding.

In women with menorrhagia, the administration of estrogens (that work, at least in part, by elevating VWF and FVIII levels) often results in significant clinical benefit.

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.

Desmopressin use in von Willebrand disease
Desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) is a synthetic analogue of the antidiuretic hormone vasopressin. Although the precise details of its mechanism of action in elevating plasma VWF and FVIII levels have yet to be determined, there is evidence that the...
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molecule is a specific vasopressin V2 receptor agonist, and that following binding to this receptor on endothelial cells, a cAMP-mediated secretory pathway is initiated. There is now more than 25 years of clinical experience with desmopressin in treating VWD; intravenous, subcutaneous, and intranasal routes of administration have all been extensively utilized [20]. 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. Because some patients feel light-headed following administration, the agent is best given with the patient sitting or lying down. Due to the mild antidiuretic effect of the agent, fluid intake should be regulated 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. The agent 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. Type 3 patients are extremely unlikely to show any benefit from desmopressin administration since most synthesize no intrinsic VWF. In fact, some patients will develop alloantibodies against the VWF in therapeutic concentrates. In type 2B patients, desmopressin may exacerbate the associated thrombocytopenia. 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, a recent large prospective study of the biological response to desmopressin has shown that only 27% of type 1 and 18% of type 2 VWD patients demonstrated a satisfactory increment of VWF levels, and a shortening of the bleeding time [21]. Given the currently 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. Another very recent observation is that the VWF circulating half-life may be significantly shortened in some cases of type 1 VWD, thus resulting in an abbreviated DDAVP response [22]. This observation also suggests that a 4-hour time point of assessment in the DDAVP therapeutic trial is advisable.

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 (approximately 70% of the initial VWF and FVIII increments) [23].

VWF/FVIII concentrate use in von Willebrand disease

For 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, VWF and FVIII levels can be restored by the infusion of plasma-derived concentrates of these proteins. The inability to eliminate viruses from cryoprecipitate (the previous blood product of choice for VWD), and the current lack of any licensed recombinant VWF concentrate, has resulted in the extensive use of several plasma-derived VWF/FVIII products [24-28]. These products have been shown to be free of transfusion-transmitted infectious agents (apart from rare parvovirus B19). There is some concern about the products’ potential for provoking venous thrombosis, but this complication is also very infrequent. Where venous thrombotic events have been documented, it has been suggested that supra-normal FVIII levels may have played a pathogenic role.

The major issues that remain unresolved with regards to the utilization of these concentrates relate to the appropriate dosing schedules and the identification of laboratory tests that best mirror the clinical benefit of the products.

The potency of these concentrates is now variously designated by either their FVIII:C and VWF:RCo contents. While there is evidence that the plasma level of FVIII:C is the major determinant of hemostasis during surgery, the role for determining the concentrate dosage based on VWF:RCo units is less clear. Similarly,
while the measurement of FVIII:C levels during peri-operative periods provides some level of confidence in the hemostatic response, there is no evidence that the bleeding time provides any useful assessment of treatment efficacy.

Systematic assessment of prophylactic regimens of treatment in VWD is limited [28]. Nevertheless, there is a sense that some patients with type 3 VWD or severe type 1 disease have sufficient problems from mucosal bleeding, or joint and soft tissue bleeds, that regular prophylactic therapy would be justified.

While current treatments for VWD are both effective and safe in most instances, there are clearly opportunities for additional therapeutic advances. These might include the future use of interleukin-11 as a complement to desmopressin administration, and the production of a recombinant VWF concentrate. It appears likely that at least one of these products will enter clinical trial in the near future.

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