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Von Willebrand Disease

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Von Willebrand Disease

Introduction

Erik Von Willebrand was an internist who in the late 1900s took an interest in blood. More specifically, he was interested in learning more about the blood's ability to clot. Throughout his works, Erik Von Willebrand identified a new disease. He stated it was quite different from hemophilia and similar blood-clotting diseases in that this new disease had characteristically extended time of bleeding. In some cases, this prolonged bleeding was life-threatening (1). This new disease would go on to be named after him, Von Willebrand Disease (VWD). A few years later, the gene affected by the disease was identified and similarly named Von Willebrand Factor (VWF). VWF plays an important role in blood clotting because it promotes platelet adhesion by binding to components of connective tissue, glycoproteins on platelet surfaces, and clotting factors (2). To date, three types of VWD exist, each one dependent on VWF levels and progressively more severe. Nevertheless, the most common VWD symptoms are abnormal bleeding, blood in stool or urine, and excessive bleeding (3).

Incidence

According to 2015 statistics from the Center for Disease Control, VWD affects over 3 million people in the United States alone (4). This is a number larger than the population of 21 of the 50 states of the United States. Along with hemophilia, VWD is the most common inherited bleeding disorders that are found in hospital emergency rooms (5). Also, a report

from the US Hemophilia Treatment Center recorded that from 1990-2010 VWD cases increased by 148% (6).

Genetic Basis

As previously stated, VWF is the main protein affected in VWD. The DNA sequence for VWF is found on chromosome 12; specifically, it is on the p13.3 location. The sequence is on the negative DNA strand and is 175,797 base pairs long. The mRNA transcribed, in turn, is 8833 base pairs long, consisting of 51 introns and 52 exons. The final translated VWF protein is composed of 2,813 amino acids (7).

Domains. To understand both the importance and functionality of VWF it is paramount to understand its protein domains. VWF protein is composed of fourteen domains in the following order: D1-D2-D-D3-A1-A2-A3-D4-B1-B2-B3-C1-C2-CK (8). The first four domains (D1, D2, D, and D3) serve in regulating the formation of multimers (multiple monomers held together through noncovalent bonds). From these, the D and D3 domains allow VWF to bind to Coagulation Factor VIII (FVIII) protein. FVIII is carried by VWF throughout the bloodstream in its inactive form. When vascular injury occurs and coagulation is needed, it is released from VWF into the affected area where it forms the FVIII/FIX complex needed for coagulation (9, 10). The A1 domain of VWF allows the protein to bind GpIb. GpIb is a glycoprotein found on the surface of platelets. The interaction stabilizes platelets and in turn facilitates the interaction between platelet receptors and their ligands (11). The A3 domain is responsible for binding to collagen. Collagen is found in the subendothelial layers of blood vessels. This allows VWF to anchor itself to the walls of blood vessels during vascular injury. Altogether, the domains found on the VWF allow it to carry FVIII to the site of vascular injury, anchor itself to collagen on blood vessel walls, and promote

aggregation of platelets for coagulation to occur. Figure 1 summarizes the functions of the VWF domains.

Pathophysiology

Single-Nucleotide Mutations

Recent research has vastly aided in identifying a great range of genetic defect that have direct implications on the phenotypes of the different types of VWD. As discussed in the next section, VWD type 1 is the most common of all the types of VWD. For VWD type 1, missense mutations account for approximately 80% of the mutations that lead to the VWD type 1 phenotype. Missense mutations occur when there is a single nucleotide substitution in the DNA code. This change of a nucleotide results in a codon that codes for an amino acid different from the one coded by the non-mutated sequence (13). At least half of these VWD type 1 missense mutations occur in exons 18-28. For example, in the normal, unmutated sequence in base pair 3639 codes for the amino acid cysteine. In some cases, a missense mutation of the cysteine results in a change from cysteine to guanine (C1130F mutation). This particular mutation has been well documented in VWD type 1 (14). This phenomenon does not only occur in VWD type 1. In VWD type 2 similar missense mutations are responsible for the diseased phenotypes. Different types of missense mutations have been linked to VWD type 2A, 2B, and 2N.

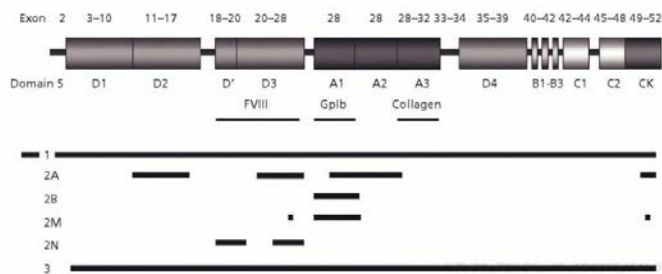


Fig. 1. The structure of VWF including domains and common locations of gene mutations of each type of VWD (12).

However, missense mutations are not the only causes of VWD. Null mutations, in which there is a loss of function of the protein, such as deletion mutations and nonsense mutations have been identified to account for 90% of the genetic and molecular defects observed in VWD type 3. When a deletion occurs, a segment of the DNA sequence is lost. This can occur in the form of loss of a single nucleotide or of loss of a larger portion of the DNA sequence. In VWD, especially in VWD type 3, the most common type of deletion is a loss of a single cysteine nucleotide of exon 18. This particular deletion has been observed in 48.3% of patients from Europe who were diagnosed with VWD type 3. Nonsense mutations occur when a codon that would code for an amino acid in its unaltered state is changed to a stop codon and translation is stopped prematurely. This causes a VWF protein that has not been fully translated and thus will not carry out normal functions. All of the single-nucleotide mutations previously mentioned are examples of point mutations (15).

VWF Protein Domain Mutations

In addition to point mutations, studies have linked larger mutations of VWF protein domains to the various phenotypes of VWD. For example, as previously stated, the D1 domain of VWF is involved in regulating the formation of multimers through non-covalent bonds. A study concluded that mutations which are found in the D1 domain have been shown to weaken the formation of multimers, reduce intracellular trafficking, as well as reduce the secretion of VWF from the endothelial cells of the vascular tissue to the bloodstream (16). A different study determined a similar pathological effect in which mutations of the A3 domain were found to cause VWD type 2M, a rare form of VWD type 2. The A3 domain is normally attributed to binding of collagen. When these mutations occur in the domain, however, there is a decreased VWF-dependent adhesion to platelets (17). Finally, a different

set of mutations of the A3 domain caused a significant deficiency in the ability of VWF to bind to collagen (18). Figure 1 contains information regarding where most mutations occur in the VWF sequence for each type of VWD.

Pathology

VWD Type 1

There are three main types of VWD. Of these, VWD type 1 is the most common type of VWD. While it is inherited as a trait that is autosomal dominant, the trait also has incomplete penetrance. Thus, two affected alleles must be inherited in order to produce the VWD type 1 phenotype. VWD type 1 is characterized by a partial defect in VWF protein levels in the blood. Hence, in VWD type 1 less VWF is found in circulation than what are considered appropriate levels required for normal function. This is why VWD type 1 is referred to as a partial quantitative defect of VWF. This quantitative defect itself does not pose a life-threatening risk to the affected person. However, the affected person will take significantly longer to clot a wound than an unaffected person (19).

VWD Type 2

Compared to VWD type 1, VWD type 2 is referred to as qualitative defects rather than quantitative. In VWD type 2 VWF levels are considered to be in the normal range. However, there is alteration of function of the protein. VWD type 2 is subdivided into four subtypes (Type 2A, 2B, 2M, and 2N) each of these subtypes corresponds to a different alteration of function of VWF. When VWD type 2A occurs, the affinity of VWF for platelet glycoprotein GpIb is increased. Therefore, VWF will have greater adherence to platelets and these affected VWF proteins will promote a larger platelet aggregation than would normally occur. A danger of this VWD subtype is that the augmented aggregation of platelets can

cause blockage (20).

In contrast, type 2B is characterized by a lower affinity of VWF to the platelet glycoprotein GpIb. In this case, fewer VWF proteins will bind to the GpIb glycoprotein and as a result platelet aggregation will be decreased. Therefore, the tissue exposed during vascular injury will not clot properly. Similarly, in VWD type 2N the affinity of VWF to FVIII is decreased. When this occurs, FVIII is not transported in sufficient quantities to the affected area. Therefore, VWD type 2N results in a similar phenotype as VWD type 2B. Finally, VWD Type 2M involves defects in VWF/platelet interactions. Since it is a rare form of VWD, not much studies address this particular type. Nevertheless, existing research has linked VWD type 2M to impaired binding to platelets as well as impaired binding to collagen in vascular subendothelium (21).

VWD Type 3

VWD type 3 is the most severe type of VWD. Similar to VWD type 1, VWD type 3 is a quantitative type of VWD. This type of VWD is characterized by extremely low or virtually non-existent levels of VWF in the bloodstream. Given this situation, in the presence of vascular injury clotting will be absent or exceedingly limited. This proves to be life-threatening in almost all circumstances.

Diagnosis

Although VWD is not a disease which occurs frequently, the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis stated that VWD is more than likely underdiagnosed (22). Considering that bleeding symptoms are quite common within even the unaffected population, VWD is difficult to properly diagnose. However, certain predictors exist. For example, it has been documented that 47-60% of

women who reported menstrual periods with prolonged and/or heavy bleeding (menorrhagia) were later diagnosed with VWD. This was most prevalent in VWD type 3. Similarly, epistaxis (nose-bleeds) was a highly reported symptom (55%) by people who would later be diagnosed with VWD. Other symptoms frequently found in patients who are later diagnosed with VWD include bleeding after a dental extraction and ecchymoses (skin discoloration that is normally caused by bleeding that occurs underneath). Figure 2 indicates where these symptoms normally occur in the human body.

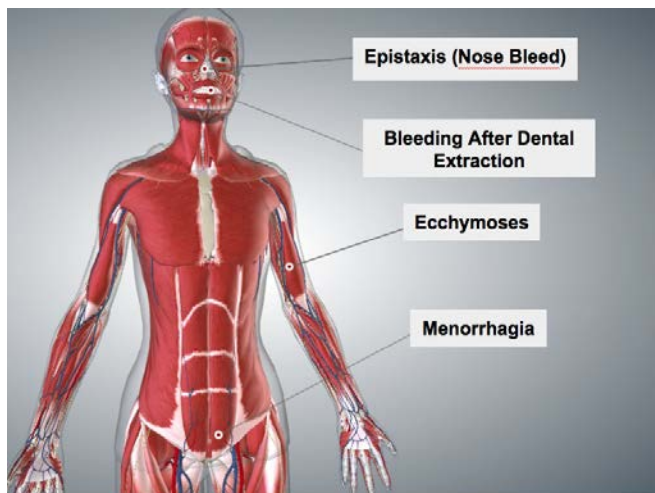


Fig. 2. The location of the four most common symptoms of VWD. Epistaxis occurs in the nose, bleeding occurs in the oral cavity during dental extraction, ecchymoses frequently occur in the limbs due to bruising, and menorrhagia occurs only in women during menstrual periods as blood exits the vagina.

When making a diagnosis it is important to identify these and other common symptoms as well as a personal and family history to assess the likelihood of the disease. Once these steps have been done, a physical examination may be performed. The physical examination itself should be done to 1) confirm evidence of recent bleeding and 2) find other probable causes of such bleeding. Evidence for recent bleeding include petechiae, hematomas, and ecchymoses among others. Other probable causes of bleeding that are looked for in the

physical examination include arthropathy, laxity of joint and skin, signs of anemia, splenomegaly, evidence of liver disease, lesions present in gynecologic examination, and telangiectasia (23).

Laboratory

To date, there is no single laboratory test available that can screen for VWD. However, to further confirm the diagnosis of VWD the first step is to do an initial evaluation of hemostasis. These tests will only provide the physician with an idea of whether the symptoms may be due to a deficiency in platelets (thrombocytopenia) or a deficiency in coagulation factors. There are three tests that are performed in this step: a partial thromboplastin time (PTT), a platelet count and complete blood count (CBC), and prothrombin time (PT). In addition, an optional fibrinogen level or a thrombin time (TT) test can be done. If no abnormalities are present in the test results or if there is a strong history of bleeding, the initial VWD assays are performed.

The initial VWD assays are used in detecting VWD or low VWF. Each of the three tests in step measure different aspects related to the disease. The VWF:Ag assay measures the amount of VWF protein present in blood plasma; the VWF:RCo assay measures the function of VWF when in it participates in ristocetin cofactor activity; and the FVIII assay measures the ability of the VWF protein to serve as a carrier protein for FVIII. If an abnormality is found in any of the tests, VWD is the most likely diagnosis and referral to a coagulation specialist is recommended.

Treatment and Management

Treatment available to treat VWD is quite limited. Not enough research has been conducted in terms of treatment due to the fact that there are not as many cases as other

major diseases. Nevertheless, throughout the years there have been successful medications in providing temporary relief of VWD symptoms.

Currently, the most widely used medication for treating VWD is desmopressin (DDAVP). Desmopressin has been used for over twenty years to treat VWD.

Desmopressin works by binding to receptors on endothelial cells of blood vessel walls. This causes the cascade release of the secondary messengers cyclic adenosine monophosphate. The cascade then induces the exocytosis of VWF from the WeibelPalade bodies of endothelial cells where VWF is stored. This mechanism also releases the VWF cargo protein FVIII. Therefore, VWF and FVIII are then released into circulation and carry out their normal functions (24).

While desmopressin allows only temporary relief of VWD symptoms, it has proven effective in reaching an appropriate level of important blood proteins. Desmopressin is used for treating patients of VWD in a number of scenarios. For instance, desmopressin can be used by patients of VWD who suffer from a bleeding gum. Desmopressin can also be used by a VWD patient who will undergo a wisdom teeth surgery and there is significant bleeding involved. In more serious scenarios, desmopressin is used by VWD patients during major surgeries to prevent complications due to loss of blood and to promote proper healing.

Since desmopressin is only a temporary solution to VWD, patients must learn to manage the disease. VWD patients are recommended not to participate in contact sports as these may lead to bleeding or internal injuries. Depending on the severity of the disease many VWD patients are advised to have a dose of desmopressin available in case of emergency. However, desmopressin is available only by prescription. In addition, desmopressin can cost over \$730 for 100 0.1 mg tablets and over \$1,000 for 100 0.2 mg tablets (25).

Current Research

ADAMTS-13 is a protein that has the ability to breakdown large and complex molecules or proteolysis. Specifically, the protease ADAMTS-13 targets the VWF protein for degradation. Researchers have then studied ADAMTS-13 and its role in VWD. These researchers have found that inhibiting this VWF protease ADAMTS-13 yielded two results. First, they found that the inhibition of ADAMTS-13 lead to less degradation of VWF, as expected. Surprisingly, the researchers also found that this ADAMTS-13 inhibition actually lead to improved function of VWF. Research continues along this field as it may prove to become a novel treatment for VWD (26).

Another type of innovative research that is being conducted studies the effects of lung transplants on VWD. These researchers used pig models to study VWD. They performed lung transplants from control pigs to the pigs with the deficiency in VWF. The studies they performed indicated that the pigs with low levels of VWF had significantly higher levels of VWF after the surgery had been performed. The researchers were then able to conclude that the reason for this occurrence is that the endothelial cells of the lungs naturally secrete high levels of VWF (27). Research in this field continued and in 2015 a lung transplant was performed in Spain on a 26-year old male with VWD type 1. The study found that the levels of VWF in the blood increased during the days after the surgery. Surprisingly, the VWF levels did not only increase post-surgery. Laboratory tests conducted during the months and years following the surgery showed that these levels of VWF were maintained. This is the first documented case of VWD having been corrected through a transplantation of the lung (28).

Summary

VWD is a systemic, hereditary disease characterized by reduced levels of VWF in the

bloodstream or loss of function of the VWF. VWD can present itself in three main types (VWD type 1, 2, and 3) as well as four subtypes of VWD type 2 (VWD type 2A, 2B, 2N, and 2M). VWD types 1 and 3 are characterized by reduced or severely reduced levels of the VWF protein in the blood, respectively. VWD type 2 and its subtypes are associated with loss of function of VWF. Mutations of the DNA code account for most the causes of all types of VWD. Diagnosis of VWD involves a detailed family and personal history that could indicate a hereditary disease, a physical examination to confirm recent bleeding and possible causes, an initial examination of hemostasis that might indicate other causes, and a set of initial VWD assays that could determine low levels of VWF protein in blood plasma.

Desmopressin is the most common treatment for VWD. Desmopressin temporarily induces exocytosis of VWF into the bloodstream. Also, research is being conducted to provide a better understanding of VWF-related proteins (ADAMTS-13) and of long-term treatment for VWD.

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