INTRODUCTION

Von Willebrand disease, also known as VWD, is the most common hereditary blood clotting (coagulation) abnormality described in humans - in other words, it is the most common inherited bleeding condition. Von Willebrand disease, however, can also result from other medical conditions. The patient suffers from extended or excessive bleeding. The bleeding may sometimes damage internal organs, and even cause death, although this is rare.¹

VWD may arise from a quantitative or qualitative deficiency of vWF (von Willebrand factor), a multimeric protein that is required for platelet adhesion - i.e., patients either have low levels of that protein in their blood, or the protein does not work properly. VWF is a vital component in the blood clotting process. Patients take longer to form blood clots; when they are cut it takes longer for them to stop bleeding.²

When a blood vessel is injured, small blood cell fragments called platelets will normally clump together to plug the hole in the blood vessel and stop the bleeding. VWF is a glue-like substance that helps the platelets stick together and form a blood clot. VWF also carries clotting factor VIII, a vital protein in the blood clotting process. Clotting factor VIII is either missing or faulty in patients who have haemophilia, or some other clotting disorder. The commonest type is Hemophilia A due to deficiency of factor VIII (FVIII), which is important zymogene co-factor for clot formation.³

Although von Willebrand disease is much more common than haemophilia, it is usually milder. According to the NIH (National Institutes of Health), USA, 1 in every 100 to 1,000 people in the USA is affected. While hemophilia affects males, VWD affects both sexes. Other factors, including ABO blood groups may also influence the severity of the condition. VWD is phenotypically heterogeneous and is classified into 3 different types. Type 1 refers to partial, quantitative deficiency WVF, and the more severe type 3 refers to complete deficiency. Type 2 WVD refers to qualitative abnormalities of VWF, usually measurable in normal amounts in plasma, and is further subdivided into 4 subtypes—types 2A, 2B, 2M, and 2N—based on more subtle differences in phenotype. Several VWF assays are used in the diagnosis of VWD and its subtypes, such as those that measure the plasma levels of VWF antigen (VWF:Ag), VWF binding to type I or type III collagen (collagen binding activity, vWF:CBA), and VWF interactions with the antibiotic ristocetin and platelet glycoprotein Ib (vWF:Ristocetin cofactor activity, VWF:RCOF). This large number of measurements reflects the fact that none of us by itself sensitive and specific enough for diagnosis.

Von Willebrand disease treatment focuses on preventing or stopping bleeding episodes, mainly with medications. With proper treatment patients can lead normal and healthy lives.¹²

HISTORY

The Finnish physician Erik A von Willebrand in 1926 described a dominantly inherited bleeding disorder occurring in both sexes, after having investigated a large family on the Aland Islands in the Gulf of Bothnia situated between Sweden and Finland. The first patient was a five-year-old girl, the ninth out of eleven children in family S, who presented with severe bleeding and who later died at the age of 13 during her fourth menstrual bleeding. Out of 66 additional relatives that von Willebrand was able to investigate, he found 23 to be bleeders, of whom 16 were women and seven were men. He also reviewed 27 cases reported in the literature with similar symptoms.

The disease was characterized by nose bleeding, menorrhagia, bleeding after tooth extractions, and from wounds. The bleeding time was prolonged, whereas the platelet count was normal and it soon became obvious that this disease differed from ordinary hemophilia; hence von Willebrand called the new disorder hereditary pseudo-hemophilia. In the 1950s it had become possible to measure factor VIII (FVIII) in plasma and it was shown to be lacking not only in hemophilia A patients but also in patients affected by a severe form of the bleeding disorder similar to that described by von Willebrand. It was also shown that the condition of the patients was improved after infusion of a fraction of human plasma from healthy individuals, called fraction I-0, and interestingly also after infusion of fraction I-0 derived from plasma from hemophilia A patients.⁴

When fraction I-0, later called AHF-Kabi, was administered to the patients, the bleedings stopped, the bleeding time was normalised and the concentration of FVIII in plasma increased. This treatment was first carried out successfully, in Malmo on a woman with severe VWD manifested as life-threatening bleedings. Later also the original family on the Aland Islands was treated successfully in this way. The

Keywords: Von Willebrand Disease (VWD), von Willebrand Factor (vWF), Bleeding.
Von Willebrand factor (VWF) plays an important role in primary haemostasis by binding to both platelets and endothelial components, forming an adhesive bridge between platelets and vascular subendothelial structures and between adjacent platelets at sites of endothelial injury. It also contributes to fibrin clot formation by acting as a carrier protein for factor VIII, which has a greatly shortened half-life and abnormally low concentration unless it is bound to VWF.

Von Willebrand factor circulates as a series of multimers formed from a basic dimer subunit. High molecular weight VWF multimers are the most active forms of VWF, providing multiple binding sites that can interact with both platelet receptors and subendothelial structures at sites of injury. Plasma VWF is synthesized by megakaryocytes and endothelial cells and undergoes post-synthetic processing. When released acutely from these cells, VWF contains even larger multimers than are normally observed in the circulation. Because these "unusually large" forms are prothrombotic, they are rapidly proteolyzed to the "normal" multimer size distribution as defined by a normal plasma pool.

The physiologic importance of the concentration and size distribution of VWF multimers is illustrated by the bleeding tendency that can occur in patients with von Willebrand disease (VWD). VWD is the most common inherited bleeding disorder, affecting up to 1 percent of the population as assessed by random laboratory screening. However, only a fraction of patients come to medical attention because of bleeding symptoms and are diagnosed having VWD.

**CLASSIFICATION**

These are of two forms. They are: Inherited forms and acquired form. Hereditary forms include three major types and a platelet type. The three major forms are type 1, type 2, and type 3. The international society of thrombosis and homeostasis has classified VWD based on the definition of qualitative and quantitative defects. According to this classification, type 2 VWD is again classified into four different types like type 2A, type 2B, type 2M and type 2N.

<table>
<thead>
<tr>
<th>Type of VWD</th>
<th>Epidemiology - percentage of all cases</th>
<th>Quantitative or qualitative defect</th>
<th>Genetics</th>
<th>Presentation</th>
</tr>
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<tbody>
<tr>
<td>TYPE 1</td>
<td>60-80%</td>
<td>Quantitative defect (19-45% of enzyme level present)</td>
<td>Heterozygous for defective gene -Inherited as AD</td>
<td>-Normal life span -Occasionally easy bruising and/or menorrhagia -Bleeding after dental work, major surgery</td>
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<tr>
<td>TYPE 2</td>
<td>20-30%</td>
<td>Qualitative defect - multimers abnormal or subgroups absent</td>
<td>Usually AD inheritance (rarely AR)</td>
<td>-Bleeding tendency varies -Four subtypes: 2A, 2B, 2M, 2N</td>
</tr>
<tr>
<td>TYPE 3</td>
<td>Rare - the most severe form; 1-5% of cases</td>
<td>Quantitative - levels very low or undetectable</td>
<td>Homozygous for defective gene -AR inheritance -No vWF antigen -Low factor VIII</td>
<td>-Severe mucosal bleeding -May have haemarthrosis (as in haemophilia)</td>
</tr>
<tr>
<td>PLATELET TYPE</td>
<td>Rare - fewer than 70cases described</td>
<td>Functional mutations of vWF receptor on platelet</td>
<td>Autosomal dominant</td>
<td>-</td>
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**ETIOLOGY**

It is an inherited disease where the parent carrying the gene may or may not be symptomatic. Type 1 and type 2 are inherited if the gene is passed on to the offspring from either of the parent. Type 3 is inherited only if the gene is passed from both the parents. Acquired VWD is seen in patients with auto antibodies.

**PATHOPHYSIOLOGY**

VWF is active only in high blood flow condition and shear stress. Hence the organs with extensive small vessels such as skin, uterus, and gastrointestinal tract show deficiency of the factor. The pathophysiology of different forms of VWD can be given as followed.

**INHERITED FORMS:**

**Type 1:** It is a partial quantitative defect but the clotting impairment may not be seen clearly. Genetic changes in VWF are common in severe cases whereas in milder cases of type 1 VWD, complex spectrum of molecular pathology together with polymorphisms of VWF gene may be seen. Individuals with type 1 VWD lead a normal life though they have low levels of VWF. These low levels are due to mutations that affect the gene expression. As a result of mutations, the intracellular transportation of VWF sub-units is impaired leading to severe, dominantly inherited type 1 VWD.

Type 1 VWD can also be caused by rapid clearance of VWF from the plasma of affected individuals. This decreases the cleavage time of circulating VWF multimer by ADAMTS-13. As a result, clearance shifts multimer distribution in plasma towards those that are initially secreted by the endothelial cells.
Bleeding tendency is mainly because of decreased levels of VWF. There is normal distribution of the high molecular weight multimers. Laboratory findings reveal that the ratio of activity of VWF and its antigen is proportionately decreased.

Type 2:

It is a qualitative defect where there is no change in plasma VWF levels but characterized by a structural and functional defects based on which, it is further sub-divided into four types.

Type 2A:

It is characterized by a decreased VWF mediated platelet adhesion. This is usually because of deficiency of high molecular weight multimers in the circulation. The deficiency of large multimers arises as a result of defective multimer assembly or increased cleavage of the multimers by ADAMTS-13. Defects in multimer assembly may occur due to homozygous or heterozygous mutations. These mutations result in the prevention of multimerisation in the Golgi apparatus. The activity of ristocetin co-factor is low when compared to that of von Willebrand antigen.

Type 2B:

It is characterized by a decreased level of large multimers in the plasma and a markedly increased proteolysis. Like in type 2A, the proportion of ristocetin co-factor activity is lower even in type 2B but the proteolytic activity does not affect the multimerisation in Golgi apparatus. The mutations that cause type 2B do not impair the multimer assembly but the multimers, after their secretion, get bound to the platelets after which they become cleaved by ADAMTS-13. These small multimers do not mediate effective platelet adhesion and inhibits directly the interaction of platelets with connective tissue

Type 2M:

It includes qualitative variants in which VWF dependant platelet adhesion is decreased without any deficiency of high molecular weight VWF multimers. The secretion and assembly of the multimers is almost normal. The mutations bring about a defect in the functions and result in the impairment of VWF binding to platelets. This ultimately leads to a decreased exposure of VWF to ADAMTS-13, thereby preserves the distribution of large multimers similar to that initially secreted from endothelial cells. VWF:RCo is disproportionately low when compared to VWF:Ag in most of the patients with type M VWF.

Type 2N:

In this, the variants have a marked decline in the binding affinity for factor VIII. The mutations that impair the binding affinity may be homozygous or compound heterozygous. In certain cases, both the alleles of VWF may have factor VIII binding mutations. But in most of the cases of type 2N, only one of the two alleles has the mutation while the other may express a little or no mutation. In type 2N, the level of factor VIII is lower when compared to the VWF:Ag. This led to misdiagnosis as haemophilia A. The patients should be suspected only if they have clinical symptoms of haemophilia A with an autosomal rather than x-linked inheritance.

Type 3:

It is caused by recessive mutation which leads to undetectable VWF level. Hence it is often termed as a severe form. The mutations that usually cause type 3 VWD are missense and nonsense mutations. It is characterized by severe mucosal bleeding with no detectable VWF antigen.

Acquired VWD:

In this, the function of VWF is not inherited but its antibody complex is rapidly cleared from the circulation. It has a diverse pathology. VWF normally produced and removed from the circulation by tumor cell adhesion or VWF antibody-mediated large multimer disruption or protein digestion gradually. Patients with aortic stenosis may develop VWD and may have gastrointestinal bleeding.

Epidemiology

- Prevalence is as high as 1-2% in general population on unselected screening.
- Worldwide incidence is around 125 per million with between 0.5 and 5 per million being severely affected.
- Most patient have mild cases.
- It is more common in females.
- It is more severe with blood type O.

Clinical Manifestations

The main symptoms of VWD are:

- Easy bruising
- Frequent or prolonged nose bleeds
- Bleeding from gums
- Prolonged bleeding from minor cuts
- Heavy or prolonged menstrual bleeding
- Bleeding in the upper and lower gastrointestinal tract
- Prolonged bleeding following injury, surgery, dental work or childbirth

Many people with VWD have few or no symptoms. People with more serious VWD may have more bleeding problems. Symptoms can also change over time. Sometimes VWD is discovered only when there is heavy bleeding after a serious accident or a dental/surgical procedure. More women than men show symptoms of VWD. Women with VWD often bleed more or longer than normal with menstruation and following childbirth. Some women with VWD have a lot of menstrual pain or irregular menstruation.

Blood type can play a role. People with Type O blood often have lower levels of VWF than people with Types A, B, or AB. This means people with VWD and Type O blood may have more problems with bleeding.

Diagnosis

Early diagnosis of von Willebrand disease (VWD) is important to make sure that you’re treated and can live a normal, active life. A diagnosis of VWD is based upon identification of characteristic symptoms (e.g. evidence of mucocutaneous bleeding), a detailed patient and family history, a thorough clinical evaluation, and a variety of specialized tests. Sometimes VWD is hard to diagnose. People who have type
1 or type 2 VWD may not have major bleeding problems. Thus, they may not be diagnosed unless they have heavy bleeding after surgery or some other trauma.

On the other hand, type 3 VWD can cause major bleeding problems during infancy and childhood. So, children who have type 3 VWD usually are diagnosed during their first year of life.

To find out whether you have VWD, your doctor will review your medical history and the results from a physical exam and tests.

**Medical History**

Your doctor will likely ask questions about your medical history and your family's medical history. He or she may ask about:

- Any bleeding from a small wound that lasted more than 15 minutes or started up again within the first 7 days following the injury.
- Any prolonged, heavy, or repeated bleeding that required medical care after surgery or dental extractions.
- Any bruising with little or no apparent trauma, especially if you could feel a lump under the bruise.
- Any nosebleeds that occurred for no known reason and lasted more than 10 minutes despite pressure on the nose, or any nosebleeds that needed medical attention.
- Any blood in your stools for no known reason.
- Any heavy menstrual bleeding (for women). This bleeding usually involves clots or lasts longer than 7 to 10 days.
- Any history of muscle or joint bleeding.
- Any medicines you've taken that might cause bleeding or increase the risk of bleeding. Examples include aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), clopidogrel, warfarin, or heparin.
- Any history of liver or kidney disease, blood or bone marrow disease, or high or low blood platelet counts.

**Physical Exam**

Your doctor will do a physical exam to look for unusual bruising or other signs of recent bleeding. He or she also will look for signs of liver disease or anemia (a low red blood cell count).

**Diagnostic Tests**

No single test can diagnose VWD. Your doctor may recommend one or more blood tests to diagnose the disorder. These tests may include:

- Von Willebrand factor antigen. This test measures the amount of von Willebrand factor in your blood.
- Von Willebrand factor ristocetin (ris-to-SEE-tin) cofactor activity. This test shows how well your von Willebrand factor works.
- Factor VIII clotting activity. This test checks the clotting activity of factor VIII. Some people who have VWD have low levels of factor VIII activity, while others have normal levels.
- Von Willebrand factor multimers. This test is done if one or more of the first three tests are abnormal. It shows the structure of your von Willebrand factor. The test helps your doctor diagnose what type of VWD you have.
- Platelet function test. This test measures how well your platelets are working.

You may have these tests more than once to confirm a diagnosis. Your doctor also may refer you to a hematologist to confirm the diagnosis and for followup care. A hematologist is a doctor who specializes in diagnosing and treating blood disorders.10,11

**TREATMENT**

Reducing the risk of bleeding — If you are diagnosed with von Willebrand disease (VWD), your healthcare provider may recommend that you avoid medications that inhibit clotting or “thin the blood.” These might include aspirin and medications known as NSAIDs, such as ibuprofen (sample brand names: Advil, Motrin) and naproxen (brand name: Aleve). If you need a medication for pain or fever relief, acetaminophen (brand name: Tylenol) is a good alternative to aspirin and NSAIDs. In addition with pharmacologic interventions, the natural remedies like intake of Wheat grass juice may be beneficial in process of clotting, which will be helpful in bleeding episodes.12

Depending on the severity of your VWD, you may also have to take special precautions to avoid injuries, such as avoiding contact sports. However, precautions are not necessary for most people with type 1 and those with milder forms of type 2 VWD.

If you learn that you need a medical procedure or surgery, including dental surgery, you should discuss your VWD with your healthcare providers ahead of time. Your type of VWD, previous history of bleeding, and options to control bleeding will be discussed.

- People with VWD will generally need closer-than-average monitoring during and after surgery.
- Some people will not need any additional treatment.
- Some people can be treated with a medication called DDAVP (also called desmopressin; sample brand name Stimate). This medicine helps your body release extra von Willebrand factor into the bloodstream. However, this effect lasts only for a day or two and may not be sufficient for some people. The only way to know if it will work for you is to do a test after your diagnosis is established and when you are not bleeding; during the test, you are given a dose of DDAVP and your blood is checked before and after the dose to see if it helped. DDAVP can be given as an injection or a nose spray. If you are a person who is helped by the DDAVP nose spray, it is important to use the form intended for VWD (there are other forms intended to treat other conditions, such as fluid disorders or bedwetting). It is also important not to drink too much water, as DDAVP can cause water retention that can cause serious symptoms. Some people with heart disease may also need to avoid using DDAVP.
- Individuals with VWD may be treated with a medication that prevents blood clots from dissolving. Examples of these types of medications include aminocaproic acid (brand name: Amicar) and tranexamic acid (brand name: Cyclokapron). These medications can be given in pill form, as a mouthwash, or as an injection into a vein. These medications are especially useful for managing bleeding from mucosal surfaces, such as nosebleeds or bleeding from the mouth following dental work, and they are often given in addition to other treatments for VWD.
- Some people will also benefit from application of a foam or gel to the bleeding site that stimulates clots to form right at that spot.
- Some people will need a stronger treatment such as administration of von Willebrand factor; these products are prepared from human plasma or produced in a laboratory. Examples of plasma-derived product brand names include Humate P, Alphanate, Koate,
and Wilfactin. An example of a product manufactured in the laboratory is Vonvendi. These treatments are injected into a vein, generally in the hospital or a healthcare provider's office.

- People with acquired VWD often benefit with improvement in their VWD when they are treated for an associated condition such as an autoimmune disease or cancer or other underlying condition. The other measures listed above, and some additional medications, may also be given.

- **Treatment of severe bleeding**
  
  If you are in an accident or have severe bleeding with surgery despite receiving the treatments above, you may be given platelet transfusions and other medications in addition. It may be necessary to receive treatment for several days when severe bleeding occurs. It is important to carry information about your VWD, including what type of VWD you have, and a list of any other medical problems and medications, on a medical identification card or bracelet. This will help your healthcare providers know what type of treatment is likely to work best for you.

- **Treatment for control of menstrual bleeding** —
  
  Women with VWD who have especially heavy periods are sometimes treated with hormones, such as birth control pills or a progestin-releasing intrauterine device (IUD). These treatments can reduce heavy menstrual bleeding.

- **Treatment during pregnancy and childbirth** —
  
  Most women with VWD who become pregnant have a normal pregnancy without any complications. However, as with surgery, it is important to have proper monitoring and to know what treatments will work well for you if you do have excessive bleeding. If you get pregnant or want to try to get pregnant, you should discuss your VWD with your healthcare provider. A specialist with expertise in managing pregnancy in people with VWD should be involved.

  These discussions will help your healthcare providers develop a plan to control your bleeding before it becomes a problem. Women with VWD should be monitored closely throughout pregnancy to make sure that bleeding does not become an issue. Most will not need treatment while they are pregnant because von Willebrand factor production naturally rises during pregnancy. After delivery, however, levels of the protein can drop and lead to serious bleeding. Because of this, you may need to take one or more of the treatments described above for one to three weeks following delivery.

  A clinician with expertise in genetics counseling or a provider with expertise in the genetics of VWD can help you determine the likelihood that your child will inherit VWD. For most types of inherited VWD, the chance of a child inheriting the condition is about 50 percent. A pediatrician can discuss with you whether and when your child needs to be tested.

**Indirect Treatments**

- In addition to treatments that directly increase VWF levels, individuals with VWD often benefit from indirect haemostatic treatments, including:
  
  - Fibrinolytic inhibitors (i.e., tranexamic acid for treatment or prevention of bleeding episodes);
  - Hormonal treatments (i.e., the combined oral contraceptive pill for the treatment of menorrhagia).

**Treatment by VWD Type**

**Type 1 VWD**

Treatments that directly increase VWF levels (e.g., desmopressin or VWF/FVIII clotting factor concentrates) are usually only needed for the treatment or prevention of severe bleeding, as with major trauma or surgery. Indirect treatment with fibrinolytic inhibitors or hormones is often effective.

**Type 2A VWD**

Treatment with clotting factor concentrates is usually only required for the treatment or prevention of severe bleeding episodes such as during surgery. Responsiveness to desmopressin is variable and should be confirmed prior to therapeutic use. Indirect treatments can be beneficial.

**Type 2B VWD**

Clotting factor concentrates are usually required to treat severe bleeding or at the time of surgery. Treatment with desmopressin should be undertaken cautiously as it can precipitate a worsening of any thrombocytopenia. People with certain pathogenic variants associated with mild or atypical 2B VWD, however, do not appear to develop thrombocytopenia when exposed to desmopressin. Indirect treatments (i.e., fibrinolytic inhibitors) can be useful.

**Type 2M VWD**

Because desmopressin response is generally poor, VWF/FVIII concentrate is the treatment of choice.

**Type 2N VWD**

Desmopressin can be used for minor bleeding, but because the FVIII level will drop rapidly (as FVIII is not protected by VWF), concentrate containing VWF as well as FVIII is required to cover surgical procedures.

**Type 3 VWD**

Treatment often requires the repeated infusion of VWF/FVIII clotting factor concentrates. Desmopressin is not effective in type 3 VWD. Indirect treatments may also be beneficial.

**Pediatric Issues**

Special considerations for the care of infants and children with VWD include the following:

- Infant males should be circumcised only after consultation with a pediatric hemostasis specialist.
- Desmopressin should be used with caution, particularly in those under age two years, because of the potential difficulty in restricting fluids in this age group.
- VWF levels are higher in the neonatal period; thus, phenotypic testing for milder forms of VWD should be delayed until later in childhood.
Long-Term Outlook for Those With Von Willebrand Disease

Most patients with type 1 von Willebrand disease are able to live normal lives with only mild bleeding issues. Those with type 2 are at greater risk for complications and experience mild to moderate bleeding. These individuals may suffer worse bleeding in the case of infection, surgery, or pregnancy. Individuals with type 3 are at risk for severe bleeding as well as internal and gastrointestinal bleeding. In all cases, people living with von Willebrand must take caution to warn health providers, including their dentists, of their condition. Your family and close friends should also know of your condition in case of an unexpected accident and/or the need for life-saving surgery.15

COMPLICATIONS IN PREGNANCY

Pregnancy in von Willebrand’s disease may carry a significant risk of bleeding. Information on changes in factor VIII and von Willebrand factor and pregnancy outcome in relation to von Willebrand factor gene mutations are very scanty. A woman with VWD should consult a hematologist and specialized obstetrician on becoming pregnant. She will probably have blood tests during the last trimester.16

PREVENTION OF BLEEDING EPISODES FOR PATIENTS WITH VWD

To prevent bleeding episodes, people with vWF should check with a physician before taking medications, and they should avoid over-the-counter (OTC) medications that may affect blood clotting, such as aspirin, ibuprofen, and other NSAIDs. They should also inform health care professionals, including dentists, and sports coaches about their condition. People with severe symptoms should wear a medical ID necklace or bracelet. To minimize common health risks, people with vWD should eat a healthy, balanced diet, and exercise regularly. Normally, vWD does not interfere with daily activities, but children may be advised to avoid contact sports, like football and hockey.15

CONCLUSION

VWD may arise from a quantitative or qualitative deficiency of vWF (von Willebrand factor), a multimeric protein that is required for platelet adhesion - i.e., patients either have low levels of that protein in their blood, or the protein does not work properly. Treatment of VWD mainly focuses on preventing bleeding complications with invasive procedures or promptly treating bleeding episodes. Most people with VWD only have occasional and mild bleeding problems. Others may bleed more often or sometimes have a more serious bleeding problem, but with appropriate management, these bleeding episodes can be controlled or prevented.

REFERENCE