

von Willebrand Disease: The Diagnosis and Management of This Bleeding Disorder

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Abstract

von Willebrand disease (vWD) is one of the most common bleeding disorders, first described by Erik von Willebrand in the Aland Islands. It occurs as a result of decreased or abnormal von Willebrand factor (vWF), a factor that is needed in the process of blood coagulation; acting like a “glue” helping platelets to stick together and form the blood clot. The principal function of vWF is binding with other clotting factors (especially Factor VIII) that are also necessary in the clotting process. There are two main forms of this disease: the inherited and the acquired forms; each one's pathophysiology depends on the qualitative or the quantitative defects in vWF. The diagnosis of vWD depends on several factors: measurement of vWD antigen, vWF activity assay, the activity of Factor VIII, and some other additional tests. The management of this disease includes replacement therapy, nonreplacement therapy, and some other kinds of managements that include the use of fibrinolytics and topical agents.

Keywords: Factor VIII, platelets, von Willebrand disease, von Willebrand factor

INTRODUCTION

When a blood vessel is injured and starts bleeding, platelets together with some clotting factors form a plug at the region of injury. As a result, the blood vessel stops bleeding. The plasma protein which allows or helps the platelets to stick with each other and form a clump is the von Willebrand factor (vWF), which also carries Factor VIII. When there is a decrease in plasma levels or defect in the vWF, the ability of the blood to clot decreases, leading to a heavy and continuous bleeding after an injury, which is termed as von Willebrand disorder or disease. This may cause internal organ damage and rarely may lead to death.^[1]

von Willebrand disease is the most common inherited bleeding disorder, with a reported prevalence of approximately 1 in each 100 or 1000 persons.^[2] Quantitative defects include Type 1 vWD, with partial deficiency of vWF, and Type 2 vWD, with virtually complete deficiency of vWF. Qualitative variants include defects in multimerization, spontaneous platelet binding, defects in ligand binding with intact multimers, and defects in Factor VIII binding. Type 1 vWD is the most common, accounting for up to 85% of all vWD, while Type 2 is the least common, affecting about 1

in 1 million individuals. Qualitative variants account for the remainder of vWD patients.^[3] The possibility and reasonably high frequency of qualitative defects prevent the diagnosis of vWD with a single simple assessment of total vWF protein. The frequency of mild bleeding symptoms in the general population also makes choosing which patient to test for vWD a difficult task.^[4]

HISTORY

The disease is named after the Finnish doctor, Erik von Willebrand (1870–1949). He is the first to describe the hereditary bleeding disorder in the families in the Aland Islands. He could not identify the actual cause for the disorder but was able to distinguish it from hemophilia and other bleeding disorders.^[5]

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VON WILLEBRAND FACTOR

vWF is a large multimeric glycoprotein present in plasma. It is synthesized in Weibel–Palade bodies in the endothelium, α -granules of platelets (megakaryocytes), and subendothelial connective tissue. Its main function is to bind with plasma proteins, especially Factor VIII and coagulate blood. Factor VIII in its inactive state binds to vWF in the circulation. If it is unbound, it rapidly degrades. When vWF is exposed in the endothelium during an injury to blood vessel, it binds to collagen. When coagulation is stimulated, the platelet receptors get activated and vWF binds to these activated receptors. This occurs when there is a rapid flow in narrow blood vessels.^[6]

CLASSIFICATION OF vWD

There are two main forms of vWD: the inherited and the acquired forms. 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 such as Type 2A, Type 2B, Type 2M, and Type 2N.^[7]

EPIDEMIOLOGY

The disease prevalence is about only 1%. More often, it can be detected in women based on the bleeding tendency during menstruation. The disease may be severe in people with “O” blood group.^[8] Type 1 includes 60%–80% of the cases, Type 2 includes 20%–30%, and Type 3 accounts for <5% of all the cases. Acquired vWD occurs most often in individuals over 40 years of age with no prior bleeding history.^[9]

PATHOPHYSIOLOGY

vWF is active only in high blood flow conditions and shear stress. Hence, organs with extensive small vessels such as skin, uterus, and gastrointestinal tract show deficiency of the factor. The pathophysiology of inherited and acquired forms of vWD can be stated as follows.

Inherited form

Different mechanisms can ultimately lead to the development of this form. Genetic changes in vWF are common in severe cases, whereas in milder cases of this form, complex spectrum of molecular pathology together with polymorphisms of vWF gene may be seen. It could also be caused by rapid clearance of vWF from the plasma of affected individuals.^[10]

Decreased vWF-mediated platelet adhesion is one of the principal mechanisms of vWD. This is usually because of deficiency of high-molecular-weight multimers in the circulation. It is characterized by a decreased level of large multimers in the plasma and a markedly increased proteolysis. The mutations bring about a defect in the functions and result in the impairment of vWF binding to platelets.^[11]

One of the common mechanisms causing vWD is a recessive mutation that leads to undetectable vWF level. This results in a more severe form of the disease.^[12]

Acquired form

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 is 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.^[13]

CLINICAL MANIFESTATIONS OF THE DISEASE

Children with vWD may have symptoms that are different from those of parents carrying the gene. It is the bleeding disorder that is commonly seen in women. Menorrhagia is seen in more than 70% of women with vWD, and a half suffers from dysmenorrhea. Different types of vWD have varying degrees of bleeding tendencies (nose bleeding, bleeding gums, and easy bruising). Individuals with Type 3 vWD have a severe internal and joint bleeding, but this is an extremely rare condition.^[14]

Typically, Type 1 vWD manifests mild mucocutaneous bleeding. The most common symptoms include bruising and epistaxis. Women experience a heavy menstrual bleeding in their reproductive age and a heavy blood loss during delivery. If the vWF levels are lower than 15 IU/dl, the disease symptoms can be more severe.^[15] Type 2A vWD individuals usually manifest mild-to-moderate mucocutaneous bleeding. Whereas Type 2B typically have mild-to-moderate mucocutaneous bleeding. Thrombocytopenia may be observed which becomes worsened during stress (severe infection, surgery, and pregnancy). Like Type 2B individuals, individuals with Type 2M vWD also typically have mild-to-moderate mucocutaneous bleeding. When there is a low or absent vWF, the episodes of bleeding can be severe. Type 2N vWD symptoms are similar to those of mild hemophilia A, which include excessive bleeding at the time of surgery. Acquired vWD individuals also present with mild-to-moderate bleeding.^[16]

DIAGNOSIS

To establish the diagnosis of vWD, a well-structured bleeding history should be obtained from every individual patient. For this purpose, various bleeding scores have been developed and optimized in recent years.^[17,18] In addition, several laboratory tests have to be performed, including vWF antigen (VWF: Ag) and vWF platelet-dependent activity, as measured by the ristocetin-cofactor activity (VWF: RCo), or vWF collagen-binding activity (VWF: CB). As Factor VIII is bound in circulation to vWF, thereby protecting this factor from degradation, many patients with vWD also have reduced Factor VIII levels, which should therefore be determined in individuals suspected for vWD. In addition, vWF multimer analysis and more specific vWF tests are performed to further classify vWD into its various subtypes.^[19]

TREATMENT OF vWD

For most patients with Type 1 vWD, desmopressin is the choice of treatment. Type 1 individuals generally respond well and have a sustained normalization of vWF levels after desmopressin infusion. However, it is advised to perform a desmopressin test in all vWD Type 1 and Type 2 patients at diagnosis to determine the extent and duration of the response. In individuals diagnosed with low vWF, a desmopressin test may not be needed as it has been shown that all patients respond well to desmopressin with a prolonged rise of vWF levels.^[20]

Because treatment of vWD with desmopressin can cause side effects, especially in the elderly, including myocardial infarction and stroke, this should be balanced against the benefit of treatment.^[21]

Most Type 2 and Type 3 patients are treated with vWF concentrates. Currently, several plasma-derived vWF concentrates with or without Factor VIII are available, which may differ between various countries. Factor VIII/vWF concentrates are still most widely used and have the advantage that infusion of the concentrate leads to an immediate rise of both vWF and Factor VIII. Concentrates only containing vWF can also be used, but in emergency situations, Factor VIII concentrate should also be given to increase its levels to a therapeutic level.^[22]

The advantage of the pure vWF concentrates is that they do not lead to strongly increased Factor VIII levels after several days of treatment, as this may lead to a higher risk of venous thrombosis.^[23]

PROPHYLAXIS

The phenotypic spectrum of vWD is strongly variable. Some patients with Type 2 or Type 3 vWD have a mild bleeding tendency, whereas others experience severe bleeding problems, such as joint bleeding or recurrent gastrointestinal bleeding.^[24]

Despite the use of prophylactic treatment with factor concentrates in hemophilia patients for many decades, prophylaxis is not frequently started in vWD patients with a severe bleeding phenotype and vWF concentrates are not even licensed for prophylaxis in many countries.^[25]

Although efficacy data are largely derived from case series, recently, some prospective studies have been performed to study the value of prophylaxis in patients with severe vWD. This is important because of the potential development of arthropathy in patients with vWD after joint bleeds, which is still underrecognized in these patients.^[26]

Prophylaxis in selected patients with recurrent bleeding episodes reduces the bleeding rate in most individuals, including those with recurrent joint bleeds, therefore, prophylaxis seems to be of benefit for selected patients with severe vWD.^[27]

CONCLUSION

Despite increasing knowledge and insights into the diagnosis, pathophysiology, and management of vWD, several issues and questions still remain. This accounts both inherited and acquired forms of the disease associated with mechanical circulatory support. Despite that this review had addressed some of the disease's clinical challenges, many more are to be argued.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The study protocol and the subject information were reviewed and approved by a local ethics committee.

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Conflicts of interest

There are no conflicts of interest.

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