Von Willebrand Disease (VWD, Angiohemophilia) — Classification and Treatment

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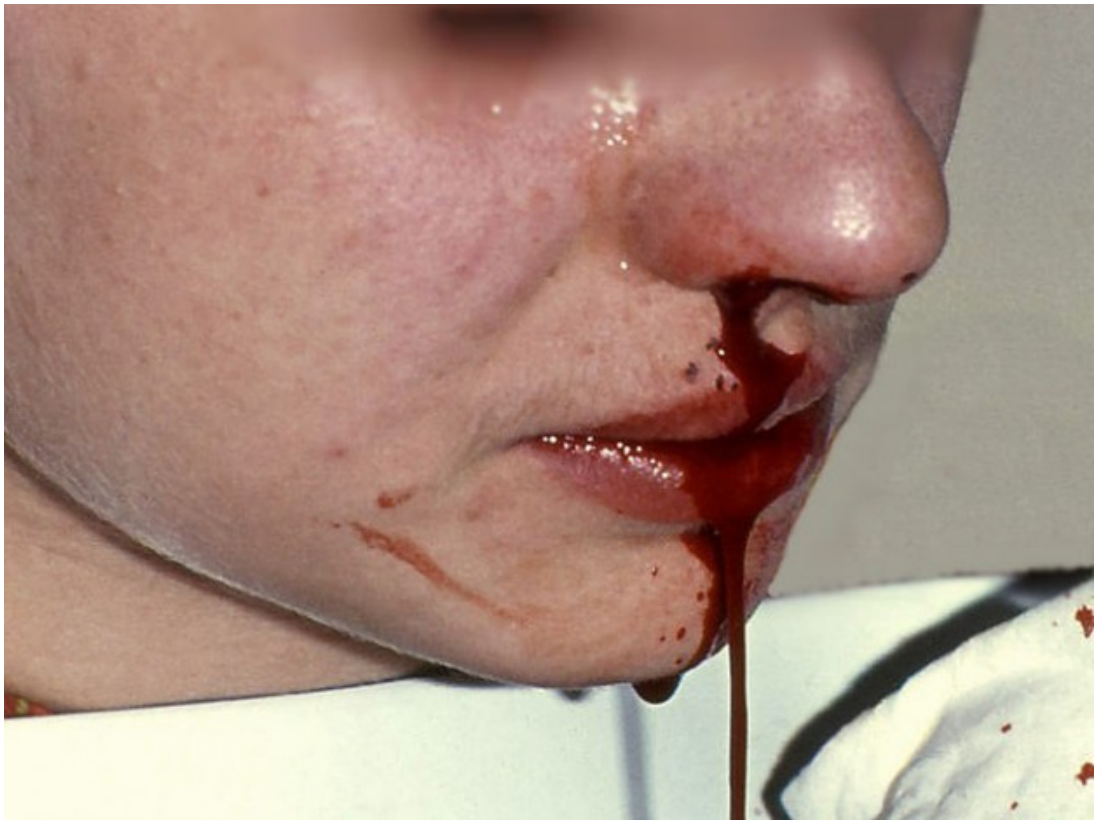
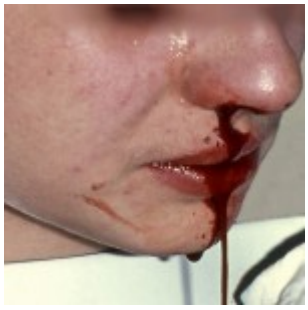
The von Willebrand disease describes a dysfunction in hemostasis concerning the primary and secondary hemostasis that has a varying clinical picture. It is the most common hereditary hemorrhagic diathesis. Taking into account the primary and secondary hemostasis, this disease excellently suits to test knowledge and comprehension of coagulation and it’s disorders.



Definition and Epidemiology of von Willebrand Disease

Increased bleeding tendency: von Willebrand disease



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Von Willebrand disease (VWD) is named after the Finnish physician, Erik von Willebrand. He examined a family that was living on the Aaland Islands in the Baltic Sea who regularly experienced severe bleeding. He jokingly called the island “Nose Bleed Island”.

He summarized the conclusions of his examination, creating a new clinical picture he called “pseudohemophilia”; thus, differentiating it from hemophilia. Over the years, this condition became known as “von Willebrand disease”.

VWD is the **most commonly inherited disorder of hemostasis** and has a relatively high prevalence (1:100). Men and women are equally affected. The disease is caused by a qualitative or quantitative **deficiency in the von Willebrand factor (VWF)** with various clinical manifestations. In order to understand the concept of this **hemorrhagic diathesis,** it is important to understand the function of VWF.

Pathophysiology of von Willebrand Disease

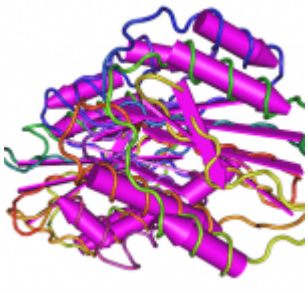

Image: “Human von Willebrand Factor” by Nevit Dilman.
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VWF is a **glycoprotein** that is produced in the **endothelium** and **megakaryocytes**, and is located in the so-called **Weibel-Palade bodies as a multimer**. It is involved in various **hemostatic processes**:

During **primary hemostasis,** VWF binds to the proteins of the subendothelial matrix and to the surface of platelets. This creates an adhesive connection between the endothelium and platelets. Glycoprotein Ib/IX on the surface of platelets plays an important role here.

As a result of the **adhesion to the platelets**, VWF activates platelet functions that result in platelet aggregation.

VWF forms a complex with **clotting factor VIII** in order to prevent its proteolytic degradation. This notably extends the half-life of factor VIII and preserves its functions.

VWF is also an **acute-phase protein** that is increasingly synthesized and secreted

during **inflammatory processes**. It spontaneously transforms into multimers in the plasma. These multimers are proteolytically degraded by the **protease ADAMTS13** which plays an important role in thrombotic microangiopathy and the hemolytic-uremic syndrome among others.

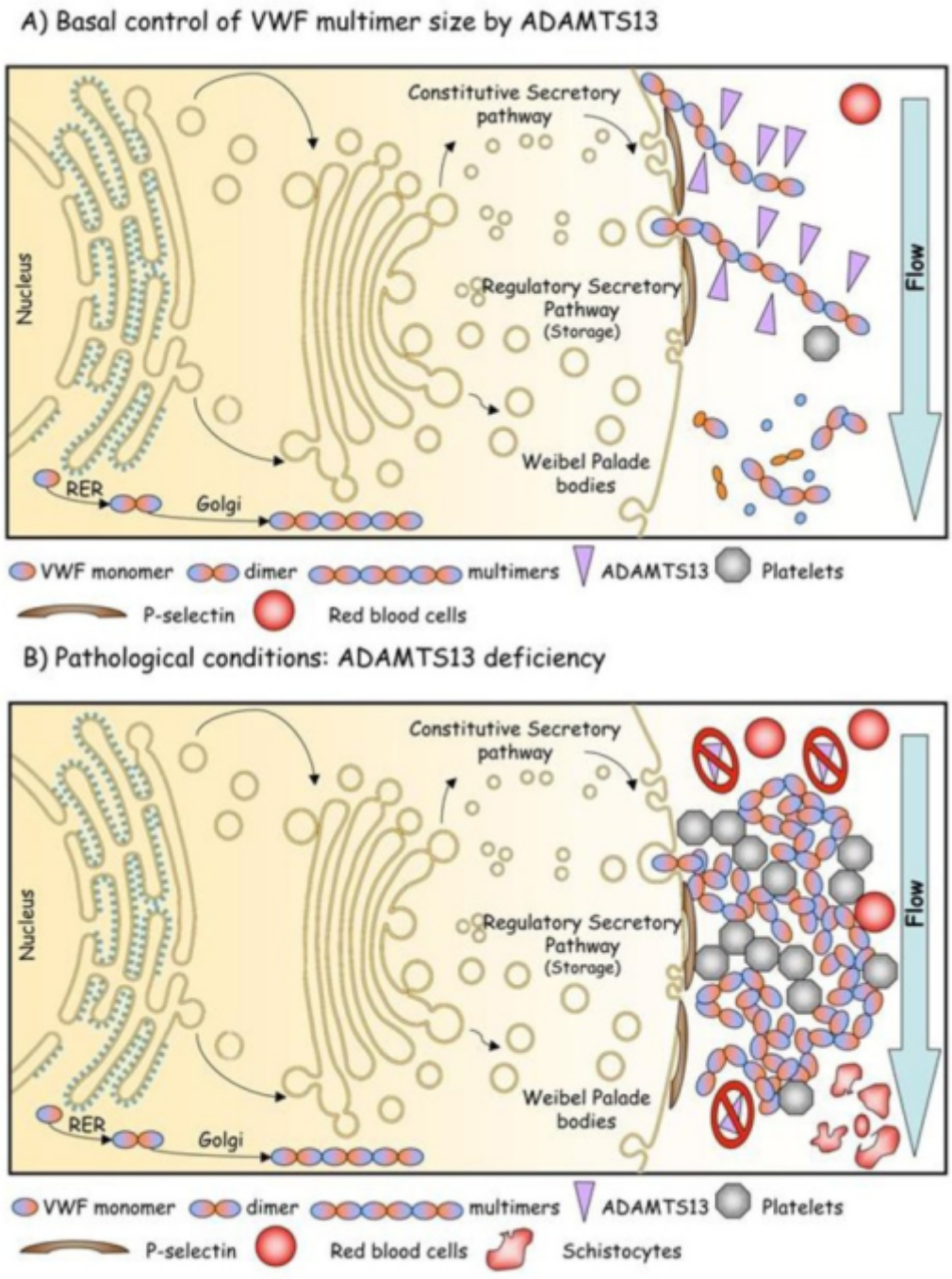

Image: “Proteolytic processing of von Willebrand factor by adamts13 and leukocyte proteases.” by Openi.
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Etiology of von Willebrand Disease

Classification of the von Willebrand disease

Many forms of vWD are hereditary:

Type 1	Autosomal dominant	75 % of patients, varies mild to severe
Type 2A	Autosomal dominant	15 % of disease, moderate
Type 2B	Autosomal dominant	5 % of disease, moderate
Platelets-Type	Extremely rare	“Gain of function” mutation results in hypercoagulability rather than bleeding
Type 2M	Rare	Normal level of vWF, but abnormal binding
Type 2N	Autosomal recessive	Low factor 8, mistaken for hemophilia in boys
Type 3	Very rare	Unmeasurable vWF, low factor VIII

Apart from this, there are many **forms of VWD that result from other underlying diseases**. In particular, **hemato-oncological diseases**, which are accompanied by increased antibody production, can cause VWD. Such diseases include monoclonal gammopathies, malignant lymphomas, and autoimmune or **myeloproliferative** diseases.

Von Willebrand disease and aortic valve stenosis

A rare but interesting phenomenon is the **frequent coincidence of symptomatic VWD in the course of an aortic valve stenosis**. This coincidence is called **Heyde’s syndrome** and is not fully understood. It is assumed that plasma VWF forms multimeric clews as described above. This formation impedes proteolytic degradation by **ADAMTS13**.

When the multimer flows through the stenotic aortic valve, the resulting mechanical stress forces it to unroll. ADAMTS13 can now perform increased proteolytic degradation and the valve size reduces, thus, impairing VWF function. The VWF multimer is inactive when degraded and is unable to perform its function in defective peripheral blood vessels. The result is VWD.

Image: “The pathophysiology of acquired von Willebrand’s Disease type 2A (vWD-2A) from an aortic stenosis (Heyde’s Syndrome).” by Michael D. Dacre. Lizenz: CC BY-SA 4.0

Note: The opposite mechanism occurs during hemolytic-uremic syndrome and thrombotic microangiopathy. A lack of ADAMTS13 causes the decreased degradation of VWF multimers. This results in the formation of platelet-rich thrombi with microangiopathy (particularly in the kidneys and brain) and consumption thrombocytopenia. This example clearly reflects the principle of balance in hemostasis. Lack of balance in such a complex system can rapidly cause increased bleeding on one hand and formation of thrombi on the other hand.

Clinical Picture of von Willebrand Disease

Symptoms of von Willebrand disease

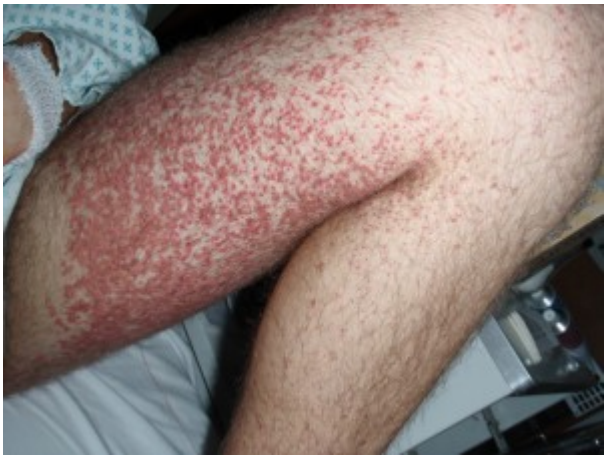


Image: “petechiae” by Peter Rammstein. License: CC BY 3.0

Although the function of VWF is very complex and integrates various processes, most patients **do not complain about symptoms or are affected by mild symptoms alone**.

The clinical picture, as described above, depends on the particular disease type. **Thrombocytic and hemophilic bleeding types** are predominant when pathological bleeding occurs (pursuant to the pathophysiology). Mucosal bleeding is typically reported. Often, the patient is unaware of the increased bleeding tendency until **increased peri- or postoperative bleeding** occurs.

Signs and symptoms are:

Easy bruising	• Spontaneous • Large • Unusual locations
Skin bleeding	• Minor lacerations with prolonged bleeding • Excessive scarring
Nose/mouth	• Frequent nosebleeds • Hard to control nosebleeds • Bleeding with tooth loss • Bleeding after brushing
Menorrhagia	• Increased bleeding with menses • Longer menses

Diagnosis of von Willebrand Disease

Genetic diagnostics of von Willebrand disease

Because of its mostly genetic origin, a detailed family medical history is pertinent. Note that in mild forms, VWD often remains undetected. The clinical bleeding type can lead to the discovery of where in the hematologic system this particular pathology is located. Laboratory results usually show a **prolonged bleeding time**, possibly a **prolongation of APTT** and a **deficiency of factor VIII**. However, VWD cannot be ruled out if APTT and factor VIII levels are normal.

A special VWD diagnosis is indicated when there is reasonable suspicion. **Definitive testing:**

- vWF antigen
- Ristocetin cofactor activity

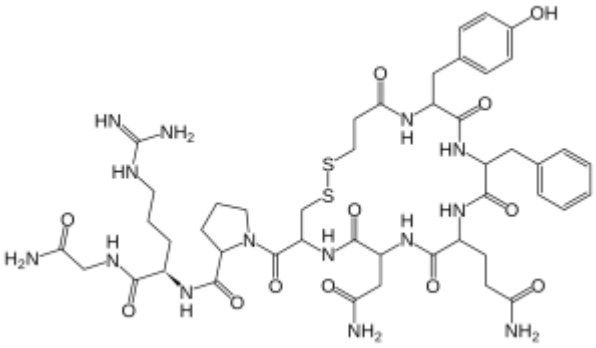
- Factor VIII level (will be different in different subtypes of disease)

Treatment of von Willebrand Disease

Therapeutic options of von Willebrand disease

Patients should, like in all cases of hemorrhagic diathesis, receive **daily prophylaxis**. If bleeding occurs or if an operation is required, it is essential to stop the bleeding completely. Acetylsalicylic acid and other antiplatelet drugs are contraindicated.

There are several **options** for pharmaceutic **treatment**:



structural formula desmopressin

Minor bleeding can be treated with **desmopressin** (analog of ADH (DDAVP)). It binds to V2 receptors and stimulates the release of VWF from the Weibel-Palade bodies. The effect of this release begins to work within 30–60 minutes and continues for several hours, so as to stop the bleeding. The effect of this medication depletes over time, therefore, its administration is limited. Desmopressin can be administered as nasal sprays or pills. Nasal sprays are a particularly good everyday option for affected children.

- If **heavy bleeding** occurs, especially peri- or postoperatively, **replacement therapy** is required. Planned replacements are advised in cases where bleeding is expected to occur. For such cases, concentrates that contain factor VIII and VWF can be given.
- Affected **women** can take **oral contraceptives** in order to reduce their menstrual bleeding and thus prevent notable blood loss.

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Notes