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 its disorders.

Definition and Epidemiology of von Willebrand Disease

Increased bleeding tendency: von Willebrand disease
Von Willebrand disease is named after the Finnish physician, Erik von Willebrand. He examined a family that was living on the Aaland islands in the Baltic sea that suffered from severe bleeding. He jokingly called the island “Nose Bleed Island”.

He summarised the conclusions of his examination, creating a new clinical picture and calling it “pseudohemophilia”, separating it from the clinical picture of a haemophilia. As time went by, this condition became known as “von Willebrand disease”.

The 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 qualitative or quantitative deficiency in the von Willebrand factor with various forms of clinical manifestation. In order to understand the concept of this hemorrhagic diathesis you should get to know the function of von Willebrand factor better.

Pathophysiology of von Willebrand Disease

The von Willebrand factor (vWF) is a glycoprotein that is produced in the endothelium and megacaryocytes and is located in the so-called Weibel-Palade-bodies as a multimer. It is involved in various processes of hemostasis:

During primary hemostasis the vWF binds to the proteins of the subendothelial matrix as well as 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 the vWF activates platelet functions that result in platelet aggregation.

The vWF forms a complex with clotting factor VIII in order to prevent its proteolytic
degradation. This extends factor VIII's half-time greatly and preserves its functions.

The vWF is also an **acute-phase protein** that is synthesised and secreted increasingly in the course of **inflammatory processes**. It forms spontaneously into multimers in the plasma. Those multimers are proteolytically degraded by the **protease ADAMTS13** that plays an important role in thrombotic microangiopathy and the hemolytic-uremic syndrome among others.

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**Etiology of von Willebrand Disease**
Classification of the von Willebrand disease

Many forms of vWD are hereditary:

<table>
<thead>
<tr>
<th>Type</th>
<th>Inheritance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Autosomal dominant</td>
<td>75% of patients, varies mild to severe</td>
</tr>
<tr>
<td>Type 2A</td>
<td>Autosomal dominant</td>
<td>15% of disease, moderate</td>
</tr>
<tr>
<td>Type 2B</td>
<td>Autosomal dominant</td>
<td>5% of disease, moderate</td>
</tr>
<tr>
<td>Platelet-</td>
<td>Extremely rare</td>
<td>“Gain of function” mutation results in</td>
</tr>
<tr>
<td>Type 2M</td>
<td>Rare</td>
<td>hypercoagulability rather than bleeding</td>
</tr>
<tr>
<td>Type 2N</td>
<td>Autosomal recessive</td>
<td>Low factor 8, mistaken for hemophilia in boys</td>
</tr>
<tr>
<td>Type 3</td>
<td>Very rare</td>
<td>Unmeasurable vWF, low factor VIII</td>
</tr>
</tbody>
</table>

Aside from this, there are many forms of vWD that result from other underlying diseases. You should keep in mind that particularly hemato-oncological diseases, that come along with 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 vDW in the course of an aortic valve stenosis. This coincidence is called Heyde’s syndrome and is not fully understood yet. It is assumed that the 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 the vWF’s function. The vWF multimer is inactive when degraded and hence not able to perform it’s actual function in peripheral, defective blood vessels. The result is a vWS.

Excursion: It’s the opposite mechanism that occurs during the hemolytic-uremic syndrome and the thrombotic microangiopathy. A lack of ADAMTS13 causes a decreased degradation of vWF multimers. This results in general 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 hemostaseology. A disbalance 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
Though the function of vWF is very complex and integrates various processes, most of the patients **don’t complain about symptoms at all or are affected by mild symptoms only**.

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 increased bleeding tendency doesn’t catch the patient’s attention until **increased peri- or postoperative after-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**

Due to its mostly genetic cause, a detailed family medical history has to be done. Though in mild forms, the vWD often remains undetected. The clinical bleeding type can lead to the discovery of where in the hemostaseologic system this particular pathology is located. Laboratory results usually show a **prolonged bleeding time**, possibly a **prolongation of APPT** and a **deficiency of factor VIII**. However, vWD cannot be ruled out if the APPT and F VIII levels are normal.

A special von Willebrand 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, perform an *everyday prophylaxis*. If there occurs bleeding or if an operation is required, it is essential to stop the bleeding completely. Contraindicated are ASA and other antiplatelet drugs.

There are several options for pharmacetic treatment:

![structural formula desmopressin]

**Minor bleeding** can be treated with *desmopressin* (= analogue to ADH, DDAVP). It binds to V2 receptors and stimulates the release of von Willebrand factor from the Weibel-Palade-bodies. The effect of this release begins to work within 30 to 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. Application of desmopressin is possible in the form of nasal sprays or pills. Nasal sprays are especially a good everyday option for affected children.

- If there occurs **Heavy bleeding**, in particular peri- or postoperative one, the patient has to be **substituted**. It is also possible to use calculated substitutions 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 weaken their menstrual bleeding and thus prevent a lot of blood loss.

Review Questions

The correct answers can be found below the references.

1. **The von Willebrand disease**...
   
   A. ...always presents itself in form of petechiae.
   B. ...always presents itself in form of sugillations.
   C. ...always presents itself in form of a purpura.
   D. ...can often take an asymptomatic course.
   E. ...always takes an asymptomatic course.

2. **You suspect von Willebrand disease in a young female patient. What leads you to this suspicion?**
A. You see teleangiectasis in the mucosa of her nose.
B. Laboratory results show prolongation of bleeding time.
C. Laboratory results show prolongation of prothrombin time.
D. Laboratory results show a shortening of prothrombin time.
E. Laboratory results show a decrease in factor IX levels.

3. You want to figure out the cause of your patient’s von Willebrand disease. Which statement isn’t true?

A. It is not necessary to do a family medical history.
B. A secondary genesis due to an underlying disease is at her young age not worth considering.
C. You apply the desmopressin test.
D. The cause is always a qualitative defect in von Willebrand factor.
E. The most common hereditary type follows an autosomal dominant inheritance pattern.

References


**Correct answers:** 1D, 2B, 3E

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