von Willebrand Disease

von Willebrand disease (vWD) is due to an inherited deficiency of von Willebrand factor (vWF). vWF is synthesized by the endothelial cell, where it is stored in Weibel-Palade bodies, and by the platelet, where it is stored in the α-granule. vWD is an extremely heterogeneous disorder that has been classified into several major subtypes. Type I vWD is the most common and is inherited as an autosomal dominant trait (See Table). This variant is due to simple quantitative deficiency of all vWF multimers. Type 2 vWD is also subdivided further dependent upon whether the dysfunctional protein has decreased or paradoxically increased function in certain laboratory tests of binding to platelets. Type 3 vWD is clinically severe and is characterized by recessive inheritance and virtual absence of vWF. The features of the three types of vWD are listed in the following table.

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
<th>Clinical Severity</th>
<th>Inheritance</th>
<th>Etiology</th>
<th>Laboratory Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>70-80%</td>
<td>Mild-moderate</td>
<td>Usually autosomal dominant Rarely compound recessive</td>
<td>Quantitative defect in vWF proteins, no structural abnormalities</td>
<td>Mild to moderately decreased vWF:Ag and FVIII</td>
</tr>
<tr>
<td>Type 2A</td>
<td>15-20%</td>
<td>Moderate-severe</td>
<td>Decreased platelet-dependent function of vWF</td>
<td>Absence of high and middle weight vWF multimers. Normal or decreased FVIII</td>
<td></td>
</tr>
<tr>
<td>Type 2B</td>
<td>Rare</td>
<td></td>
<td>Autosomal dominant</td>
<td>Structural defect of vWF with increased affinity for platelet GPIb receptor</td>
<td>Thrombocytopenia Decreased vWF activity. Absence of high molecular weight multimers</td>
</tr>
<tr>
<td>Type 3</td>
<td>Very rare</td>
<td>Severe Presents early in life</td>
<td>Variable, homozygous or compound heterozygous</td>
<td>Failure of vWF synthesis</td>
<td>Virtual absence of all vWF multimers. Very low FVIII levels (3-10%)</td>
</tr>
</tbody>
</table>

Epidemiology

von Willebrand disease (vWD) is the most common inherited human bleeding disorder. Clinically significant vWD occurs in approximately 125 people per million 1-2% of general population. However, abnormalities in vWF can be detected in approximately 8000 people per million when sensitive laboratory techniques are used, suggesting a very high incidence of subclinical disease. vWD was first described by Erik von Willebrand in 1926.
von Willebrand Disease

**Feature**

<table>
<thead>
<tr>
<th>Pattern of Inheritance (Cont’d)</th>
</tr>
</thead>
</table>

**Disease Facts**

If the history is suggestive of vWD, the first step is to perform an aPTT, platelet count, and bleeding time. Since vWF is the factor VIII:C carrier protein, low vWF levels are usually accompanied by low factor VIII:C level and a prolonged aPTT. The platelet count is usually normal and the bleeding time is frequently prolonged. However, laboratory testing in vWD is notoriously variable, particularly in mild cases, and the assays on several different occasions may be necessary to demonstrate an abnormality. In addition, the patient's blood group affects the vWF level (patients with blood group 0 have lower vWF levels than those with blood group A or B) and the other laboratory manifestations. If the initial tests confirm the presence of an abnormality, vWF levels are next measured by immunologic techniques, and vWF multimeric composition is determined by electrophoretic procedures, and the functional capabilities of vWF are determined by the ristocetin cofactor test. Ristocetin is an antibiotic, which causes platelets to express the GPIb receptor in a form in which it can be linked by vWF to cause platelet agglutination. In the assay, patient plasma is added in incremental amounts to a standard mixture of ristocetin and normal platelets and platelet agglutination is measured. Laboratory assays for vWD are outlined in the following table.

<table>
<thead>
<tr>
<th>Assay</th>
<th>Type 1</th>
<th>Type 2A</th>
<th>Type 2B</th>
<th>Type 3</th>
<th>Platelet-Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding time</td>
<td>↑ or N</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Platelet count</td>
<td>N</td>
<td>N</td>
<td>↓ or N</td>
<td>N</td>
<td>↓ or N</td>
</tr>
<tr>
<td>aPTT</td>
<td>↑</td>
<td>↑ or N</td>
<td>N or ↑</td>
<td>↑</td>
<td>N or ↑</td>
</tr>
<tr>
<td>vWF:Ag</td>
<td>↓</td>
<td>↓ or N</td>
<td>N or ↓</td>
<td>↓↓</td>
<td>N or ↓</td>
</tr>
<tr>
<td>vWF:RCo</td>
<td>↓</td>
<td>↓</td>
<td>↓, N, or ↑</td>
<td>↓↓</td>
<td>↓ or N</td>
</tr>
<tr>
<td>VIII</td>
<td>↓</td>
<td>N or ↓</td>
<td>N or ↓</td>
<td>↓↓</td>
<td>N or ↓</td>
</tr>
<tr>
<td>Multimers</td>
<td>N</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Not detected</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

*From Brandt, J.T. Laboratory Evaluation of Platelet Disorders. In McClatchey, K.D. Clinical Laboratory Medicine, 2nd Ed. Lippincott, Williams, and Wilkins, 2002.*
Desmopressin (DDAVP) is the major form of therapy for patients with Type 1 vWD. Desmopressin increases the release of vWF and factor VIII from the endothelial cell and increases endogenous plasma levels of vWF and FVIII:C by three- to fivefold. Antifibrinolytic agents and plasma products may be used in some circumstances in Type 1 vWD. FVIII/vWF plasma concentrates are the mainstay of treatment or prophylaxis for patients with Type 2 and Type 3 vWD. Recombinant factor VIII and/or recombinant activated factor VII is used in patients who have developed alloantibodies.

References


Mazurier C: Something new about type Normandy von Willebrand disease (type 2N VWD)? Thromb Haemost 92:1-2, 2004


References


