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FPIN's Clinical Inquiries

Diagnosing Von Willebrand Disease

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Clinical Question

What criteria are required to diagnose von Willebrand disease (vWD)?

Evidence-Based Answer

The diagnosis of vWD requires two clinical criteria: (1) a personal history, family history, or physical evidence of mucocutaneous bleeding and (2) a qualitative or quantitative decrease in functional activity of von Willebrand factor (vWF). (Strength of Recommendation [SOR]: C, based on expert opinion). Some patients with borderline decreased functional activity of vWF will meet the criteria for vWD if the other clinical criterion is present. (SOR: C, based on expert consensus and opinion).

Evidence Summary

vWD is the most common inherited bleeding disorder, with a 1 percent prevalence reported in a multiethnic population.¹ It can also be acquired from lymphoproliferative disorders, including monoclonal gammopathy of undetermined significance and multiple myeloma (48 percent); cardiac defects (21 percent); myeloproliferative disorders, such as essential thrombocythemia (15 percent); cancer (5 percent); autoimmune disease (2 percent); and miscellaneous sources, such as valproic acid (Depakene) use, hypothyroidism, uremia, and diabetes mellitus (9 percent).²

vWF has two primary functions: aiding blood coagulation by carrying factor VIII and protecting it from early metabolism, and helping platelets adhere to exposed subendothelial collagen at the site of vascular injury.³ vWD is classified into three types according to vWF deficiency (*Table 1*).⁵ Type 1 is a partial quantitative deficiency of vWF, although available vWF has normal function. Type 2 is a qualitative deficiency of vWF. Type 3, which is rare, includes total or near complete quantitative deficiency of vWF.

The most common symptoms of vWD include bleeding from trivial wounds lasting longer than 15 minutes; easy bruising (especially with palpable hematomas); epistaxis lasting longer than 10 minutes or requiring medical attention; oral cavity bleeding; and menorrhagia (changing a tampon or sanitary pad more than hourly, or leading to anemia or low iron levels).⁵ Knowing patients' previous responses to dental extractions, minor surgery, and trauma is helpful in making a diagnosis.⁶

A family history of vWD requires a notable history of mucocutaneous bleeding and laboratory testing compatible with vWD in one first-degree relative or two second-degree relatives.⁵

There is no single test to detect vWD. Prothrombin time, fibrinogen levels, and platelet counts are typically normal. Bleeding time is only 50 percent sensitive for type 1 vWD.⁵ The vWF antigen is used to detect quantitative deficiencies. The two tests used to assess functional activity of vWF are ristocetin cofactor activity and collagen-binding activity (*Table 1*).⁶

TABLE 1.
Laboratory Values for Von Willebrand Disease

<i>Condition</i>	<i>Description</i>	<i>vWF:RCo (IU per dL)</i>	<i>vWF:Ag (IU per dL)</i>	<i>Ratio of vWF:RCo to vWF:Ag</i>	<i>Factor VIII</i>
Type 1	Partial quantitative deficiency vWF	< 30	< 30	> 0.5 to 0.7	Normal or low
Type 2A	Decreased vWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers	< 30	< 30 to 200*	< 0.5 to 0.7	Normal or low
Type 2B	Increased affinity for platelet glycoprotein Ib	< 30	< 30 to 200*	Usually < 0.5 to 0.7	Normal or low
Type 2M	Decreased vWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers	< 30	< 30 to 200*	< 0.5 to 0.7	Normal or low
Type 2N	Markedly decreased binding affinity for factor VIII	30 to 200	30 to 200	> 0.5 to 0.7	Very low
Type 3	Virtually complete quantitative deficiency of vWF	< 3	< 3	NA	Extremely low (< 10 IU per dL)
Low vWF	Borderline deficiencies	30 to 50	30 to 50	> 0.5 to 0.7	Normal
Normal	NA	50 to 200	50 to 200	> 0.5 to 0.7	Normal

NA = not applicable; vWF = von Willebrand factor; vWF:Ag = von Willebrand factor antigen; vWF:RCo = von Willebrand factor ristocetin cofactor activity.

*— vWF:Ag is less than 50 IU per dL in most persons with type 2A, 2B, or 2M von Willebrand disease.

Adapted from National Heart, Lung, and Blood Institute. NHLBI Von Willebrand Disease Expert Panel. The diagnosis, evaluation and management of von Willebrand disease. NIH publication no. 08-5832. Bethesda, Md.: U.S. Department of Health and Human Services; December 2007. <http://www.nhlbi.nih.gov/guidelines/vwd/index.htm>. Accessed April 26, 2010.

Recommendations from Others

According to the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO), there are no absolute recommendations for diagnosing vWD

based on available evidence.⁵ Because of daily fluctuations in vWF antigen levels, the UKHCDO recommends testing patients on two separate occasions. Strenuous exercise, which falsely elevates vWF antigen levels, should be avoided for at least 10 hours before laboratory testing.⁵ The UKHCDO also created the category “possible vWD” for patients who meet some, but not all, suggested diagnostic criteria.⁷

According to the American Society of Hematology (ASH), a definitive diagnosis of vWD may be made if vWF antigen levels are less than 30 IU per dL.⁴ The ASH also describes a gray zone of 30 to 50 IU per dL, which is designated as “low vWF.”⁴ Patients with type O blood may have vWF antigen levels that fall within this range. Patients with low vWF antigen levels may benefit from desmopressin (DDAVP), which increases endothelial release of vWF antigen. If treatment with desmopressin is unsuccessful, Alphanate—a high-purity concentrate containing factor VIII and vWF—is approved by the U.S. Food and Drug Administration for the treatment of vWD.⁷

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