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von Willebrand Disease Workup

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WORKUP

Approach Considerations

Laboratory studies are directed towards documenting a deficiency of von Willebrand factor (vWF). [9, 10, 16] Levels of vWF vary with physiologic stress; in particular, plasma levels increase with estrogens, vasopressin, growth hormone, and adrenergic stimuli. Thus, vWF levels may intermittently be normal in patients with von Willebrand disease (vWD), and measurements should be repeated to confirm abnormal results.

Repeating tests at intervals of more than 2 weeks is advisable to confirm or definitively exclude the diagnosis of vWD. Optimally, testing should occur at a time remote from events that may raise vWF levels, such as pregnancy, infection, surgery, and strenuous exercise.

Screening tests typically include the following:

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- Factor VIII coagulant activity
- Ristocetin cofactor (RCoF) activity
- Concentration of vWF antigen (vWF:Ag)

Levels of vWF correlate with ABO blood type. Individuals with type O blood normally have the lowest levels of vWF, approximately 50-75% of the vWF levels found in persons with other blood types. vWF levels should be compared with an ABO blood group type–specific range from the laboratory where the test is performed.

Genetic analysis can aid diagnosis of vWD type. Newer techniques, such as next-generation sequencing, have the capacity to analyze several genes simultaneously when necessary and to identify exon deletions and duplications, which makes it possible to identify causative vWF defects in more patients than previously. Examples include discrimination of possible type 2N vWD from mild hemophilia A, discrimination of type 2B vWD from platelet-type vWD, and prenatal diagnosis of type 3 vWD. [17]

Evaluation of vWF Level and Function

vWF Activity

vWF activity (the binding of VWF to platelet glycoprotein Ib [GPIb]) has traditionally been assessed by ristocetin cofactor (RCoF) activity. In this test, ristocetin is added to a suspension of washed formalin- or paraformaldehyde-fixed platelets in the presence of the patient's plasma (as a source of vWF). The rate of aggregation is then measured using an aggregometer, a device specifically designed to monitor this activity.

The test for RCoF activity is good for evaluating vWF function, although results are difficult to standardize and the test is difficult to perform. Thus, the validity of test results should be verified when the test is performed at centers with personnel who are not accustomed to performing this test.

Normal RCoF values are 50-200 IU/dL. A level below 30 IU/dL is considered definitive for vWD, although levels of 30-50 IU/dL may be found in some patients with type 1 or 2 vWD. [9]

Newer vWF activity assays use gain-of-function GPIbα mutants that bind vWF without the need for ristocetin. This provides better precision and a lower limit of detection. These assays avoid the falsely low readings than can occur with ristocetin-dependent methods in patients with some common *vWF* polymorphisms that do not cause bleeding. [18]

vWF:Ag

This assay is usually performed (with rabbit antibody to vWF) using either a quantitative immunoassay or an enzyme-linked immunosorbent assay. A discrepancy between the vWF:Ag value and RCoF activity suggests a qualitative defect that should be further investigated by characterization of the vWF multimeric distribution. As with RCoF, a vWF:Ag level below 30 IU/dL is considered diagnostic of vWD, but levels of 30-50 IU/dL may be found in some patients with type 1 or 2 vWD. [9]

Bleeding Time, PT, and aPTT

Bleeding time

Historically, the template bleeding time was a test used to help diagnose vWD. However, this test is subject to wide variation and, with the availability of tests that provide more specific results, is not currently essential for making the diagnosis.

A prolonged bleeding time is not specific for vWD and does not help to predict whether patients without a bleeding disorder will have problematic bleeding during surgery. The test is difficult to perform, and results are difficult to confirm (ie, poor reproducibility); results frequently are normal in patients with vWD type I.

PT and aPTT

The aPTT is mildly prolonged in approximately 50% of patients with vWD. The prolongation is secondary to low levels of FVIII because one of the normal functions of vWF is to protect FVIII from degradation.

The PT should be within reference ranges. Prolongations of both the PT and the aPTT signal a problem with acquisition of a proper specimen or the presence of a disorder other than or in addition to vWD.

Workup by Type

vWD type 1

vWD type 1 can be diagnosed in a patient with significant mucocutaneous bleeding, laboratory test results compatible with vWD type 1, and a positive family history for vWD type 1. However, these criteria may be impossible to satisfy in many patients for various reasons. Therefore, physicians must acknowledge this diagnostic uncertainty and should not deny patients treatment, especially when patients' laboratory test results are compatible with vWD type 1 and the patients have either a significant history of mucocutaneous bleeding or a positive family history for vWD type I.

A less common problem is the misdiagnosis of vWD type 1 in patients who actually have a qualitative defect. The results of screening tests recommended for patients with vWD type 1 often show proportionally decreased RCoF activity and vWF:Ag in patients with vWD type 2B, although classic teaching is that a discrepancy should exist between the 2 tests. In this scenario, ristocetin-induced platelet aggregation test results should demonstrate an exaggerated affinity of the mutant vWF for platelets in the presence of ristocetin.

vWD type 2

Disproportionately low RCoF activity relative to vWF:Ag may reflect a decreased affinity of vWF for platelets. The most common cause of such loss of function is the absence of hemostatically effective large vWF multimers, characteristic of vWD type 2A. This subtype is diagnosed based on the combination of markedly reduced RCoF activity and compatible multimer gel analysis results.

In type 2B, brisk platelet agglutination occurs at low concentrations of ristocetin that have little or no effect on platelet-rich plasma from normal controls. Similar results are seen in one extremely rare disease, platelet-type vWD. In platelet-type vWD, mutations in platelet GpIb cause a phenotype similar to that of vWD type IIB.

vWD type 2M includes variants in which binding to platelets is impaired but the vWF multimer distribution is normal. Screening laboratory test findings are similar to those found in vWD type 2A, but multimer gel analysis results show that large multimers are present.

In vWD type 2N, the platelet-dependent functions of vWF are preserved, but FVIII levels are low (often < 10%). This condition is an autosomal mimic of hemophilia A, and a careful family history helps to distinguish the 2 disorders.

Multimeric examination of vWF is particularly important in the diagnosis of vWD type 2. Results from this laboratory test reveal the multimeric distribution of vWF, thus allowing classification of type 2 disease based on the specific absence of large multimers (type 2B) or both intermediate and large (type 2A) multimers.

vWD type 3

This is a recessive disorder in which vWF protein is virtually undetectable. The absence of vWF causes a secondary deficiency of FVIII and a subsequent severe combined defect in blood clotting and platelet adhesion. Results from screening assays show both absent or severely decreased RCoF activity and vWF:Ag in addition to a prolonged aPTT.

Low vWF

Guidelines from the National Institutes of Health and the United Kingdom recommend that the term "low vWF" rather than vWD be used to designate patients with an appropriate bleeding history and RCoF/vWF:Ag levels of 30-50 IU/dL. [9, 3] Such patients may nevertheless be candidates for treatment to increase vWF levels when they are at risk for bleeding. [9]

Testing for Therapeutic Options

A laboratory evaluation of a patient's response to administrations of desmopressin (DDAVP) is commonly performed to assess whether or not a patient can receive this product either therapeutically or prophylactically before surgery.

Perform a laboratory evaluation to rule out whether the patient has vWD type 2B prior to testing, in patients with risk factors for thrombotic complications, because case reports suggest this drug may be contraindicated in this setting.

Treatment & Management

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Media Gallery

of 0

Tables

Back to List

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