von Willebrand Disease: Approach to Diagnosis and Management

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QUESTIONS

1. A 30-year-old man presents with prolonged bleeding after a dental extraction. Mild hemophilia A is suspected based on a baseline factor VIII (FVIII) level of 9 IU/dL. Further testing reveals the following: genotyping is negative for a F8 mutation; a desmopressin (DDAVP) trial shows a brisk but short-lived FVIII response; von Willebrand factor antigen (VWF:Ag) level is 0.55 IU/dL and VWF ristocetin cofactor (VWF:RCo) is 0.50 IU/dL.

What is the next most useful test?

A. VWF multimer analysis
B. Low-dose ristocetin-induced platelet aggregation (RIPA)
C. VWF:FVIII binding assay (VWF:FVIIIB)
D. VWF:collagen binding assay (VWF:CB)
E. Mixing studies

2. A 23-year-old woman with type 1 VWD presents to the emergency room with an episode of epistaxis lasting over an hour. Her bleeding history includes menorrhagia requiring oral contraceptive pills and excessive bleeding post-tooth extraction. She has several family members with type 1 VWD. Laboratory testing shows a VWF:Ag level of 60 IU/dL, VWF:RCo of 55 IU/dL, and FVIII:C of 67 IU/dL.

Which of the following factors is not associated with an increase in basal VWF levels?

A. Pregnancy
B. Hypothyroidism
C. Stress
D. Active infection
E. Exercise

3. You are asked to manage a 34-year-old man with type 1 VWD who is scheduled to have 4 impacted wisdom teeth removed. Before making any recommendations, you arrange for a DDAVP trial. At baseline, his VWF:Ag, VWF:RCo, and FVIII:C levels are 20 IU/dL, 15 IU/dL, and 26 IU/dL, respectively. At 1 hour post-DDAVP administration, they are 65 IU/dL, 74 IU/dL, and 107 IU/dL. At 4 hours post-DDAVP, they are 20 IU/dL, 25 IU/dL, and 38 IU/dL. This DDAVP trial demonstrates:

A. A lack of DDAVP response
B. An adequate response to achieve hemostasis for major invasive procedures
C. Laboratory error; the trial should be repeated
D. A good DDAVP response but with a short half-life

4. Which of the following common laboratory tests will screen for the presence of VWD?

A. Activated thromboplastin time (aPTT)
B. Prothrombin time (PT)
C. Complete blood count (CBC)
D. Fibrinogen
E. None of the above

5. An 18-year-old man with type 3 VWD suffers from recurrent hemarthrosis. In the preceding 6 months, he reports 4 bleeds into his right ankle, which were treated with on-demand VWF/FVIII concentrate administration.

Ongoing management should include which of the following?

A. Regular administration of VWF/FVIII concentrates, known as prophylaxis
B. Continue with on-demand VWF/FVIII concentrates
C. On-demand DDAVP
D. The addition of platelet transfusions

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ANSWERS
1. The correct answer is (C), VWF:FVIII binding assay.
   The differential diagnosis of mild hemophilia A includes type 2N VWD. Type 2N VWD should be considered when the patient demonstrates features that are not consistent with hemophilia A: lack of an identifiable F8 mutation, an autosomal recessive pattern of inheritance, and/or short FVIII half-life with recombinant FVIII concentrates or DDAVP. Type 2N is defined by a decreased binding affinity of VWF to FVIII, and the diagnostic test is the VWF:FVIIIB assay, which will be decreased. In cases where the VWF:FVIIIB assay is not available, genotyping of the VWF gene can confirm the diagnosis. In most cases of type 2N VWD, VWF levels (VWF:Ag) and activity (VWF:RCo), multimer analysis (abnormal in type 2A and 2B), low-dose RIPA (abnormal in type 2B), and VWF:CB (abnormal with type 2A, 2B, and 2M) will be normal, and therefore these assays will not differentiate type 2N from hemophilia A. The distinction is clinically important. Patients with type 2N VWD require treatment with VWF/FVIII concentrates that will stabilize their endogenous normal FVIII, whereas hemophilia A patients require FVIII concentrates. Finally, a mixing study will identify a FVIII inhibitor and not be helpful in the diagnosis of type 2N.1,2

References

2. The correct answer is (B), Hypothyroidism. Interpretation of VWF studies requires careful consideration of the patient’s medical history, medications, and status at the time of testing. Any adrenergic stimulus, such as acute illness, stress, and exercise, can result in an increase in VWF levels and lead to a missed diagnosis. In addition, high doses of estrogen (as seen with older generation combined oral contraceptive pills) and pregnancy can significantly increase VWF levels. Therefore, testing should be avoided in stressed, ill, or pregnant patients. On the other hand, improper handling of the blood sample can result in falsely decreased VWF levels. Acquired von Willebrand syndrome (AVWS) is an acquired deficiency or defect of VWF and can complicate a number of diseases: valvular heart disease, lymphoproliferative disease, and autoimmune disease. Hypothyroidism has also been associated with AVWS, which resolves with treatment of the hypothyroidism.1,2

References

3. The correct answer is (D), A good DDAVP response but with a short half-life. The use of DDAVP versus a VWF/FVIII concentrate will depend on the observed DDAVP response and the type of surgery. DDAVP administration that increases VWF:Ag/VWF:RCo and FVIII levels to at least 30 IU/dL is adequate for most minor procedures, and VWF levels that increase well above 50 IU/dL with DDAVP administration are adequate for most major procedures. When performing a DDAVP trial, it is important to assess VWF:Ag, VWF:RCo, and FVIII levels before and at several time points after the DDAVP trial up to and including 4 hours. In our case, the patient has an adequate response at the 1-hour time point, but at 4 hours already shows significantly reduced levels. Significantly decreased levels at the 4-hour time mark may indicate increased VWF clearance, such as in type 1C VWD. The marked but short-lived response to DDAVP in type 1C may limit DDAVP’s clinical applicability for major procedures associated with high risk of bleeding; in such scenarios, VWF/FVIII concentrates are the preferred treatment.1,2

References
4. **The correct answer is (E), None of the above.** Screening tests including aPTT, PT, CBC, and fibrinogen are often performed when considering VWD to exclude the presence of other hemostatic disorders. In the majority of cases, these tests will be normal in VWD and are not appropriate screens for VWD. In rare cases, the CBC may show thrombocytopenia in type 2B VWD or the aPTT will be prolonged if the FVIII level is sufficiently reduced, as can be seen in severe type 1, type 2N or type 3 VWD.¹

**Reference**

5. **The correct answer is (A), Regular administration of VWF/FVIII concentrates, known as prophylaxis.** Patients with type 3 VWD, severe type 1 or type 2 VWD may experience recurrent joint or nasal/oral, gastrointestinal, or menstrual bleeding. Although on-demand treatment with VWF/FVIII concentrates will effectively treat bleeding episodes, the frequency of these bleeds may have a significant impact on the patient, requiring frequent hospitalization, transfusions, missed work, and, in the long-term, complications such as arthropathy. In these cases, prophylaxis improves quality of life, reduces the frequency of bleeding, need for transfusions, and hospitalizations, and prevents chronic joint disease. Over 97% of bleeds will respond to VWF/FVIII concentrates. Only in the rare refractory bleeds, transfusion of platelet concentrates may be considered. DDAVP is ineffective in type 3 VWD.¹²

**References**