COLLEGE of AMERICAN PATHOLOGISTS

Von Willebrand Disease Testing For Clinicians

SYNOPSIS AND RELEVANCE

Von Willebrand disease (VWD) is the most common inherited bleeding disorder.[1] An acquired form can be seen in patients secondary to a wide variety of illnesses including autoimmune disease, malignancies, cardiac disease, and others. VWD results from either a quantitative or qualitative deficiency in von Willebrand Factor (VWF), a plasma glycoprotein required for proper hemostasis by mediating adhesion of platelets at sites of blood vessel injury.[2-7] Clinical findings in VWD include excessive bleeding from small cuts, bleeding from mucous membranes, and easy bruising. Most patients with VWD experience mild to moderate symptoms, whereas other individuals experience no symptoms at all.

VWD is classified into the subtypes 1, 2, and 3, with Type 2 subdivided into type 2A, 2B, 2M, and 2N. Platelet mutations result in a VWD appearing disease termed Platelet Type Von Willebrand disease (PT-VWD). Proper subtyping of VWD may be challenging but is important because treatment depends on accurate classification. This module illustrates the relevant tests and appropriate algorithm to assist in diagnosis and proper subtype classification of VWD.

BACKGROUND

VWF is synthesized by endothelial cells and megakaryocytes, and circulates in the blood as a chaperone protein for Factor VIII.[4] VWF facilitates the adherence of platelets to subendothelial collagen at sites of blood vessel injury. VWF interacts with the platelet Glycoprotein Ib (GP Ib) receptor and stabilizes factor VIII in the bloodstream. Multimeric VWF is comprised of high, intermediate, and low molecular weight (HMW, IMW, and LMW) multimers.

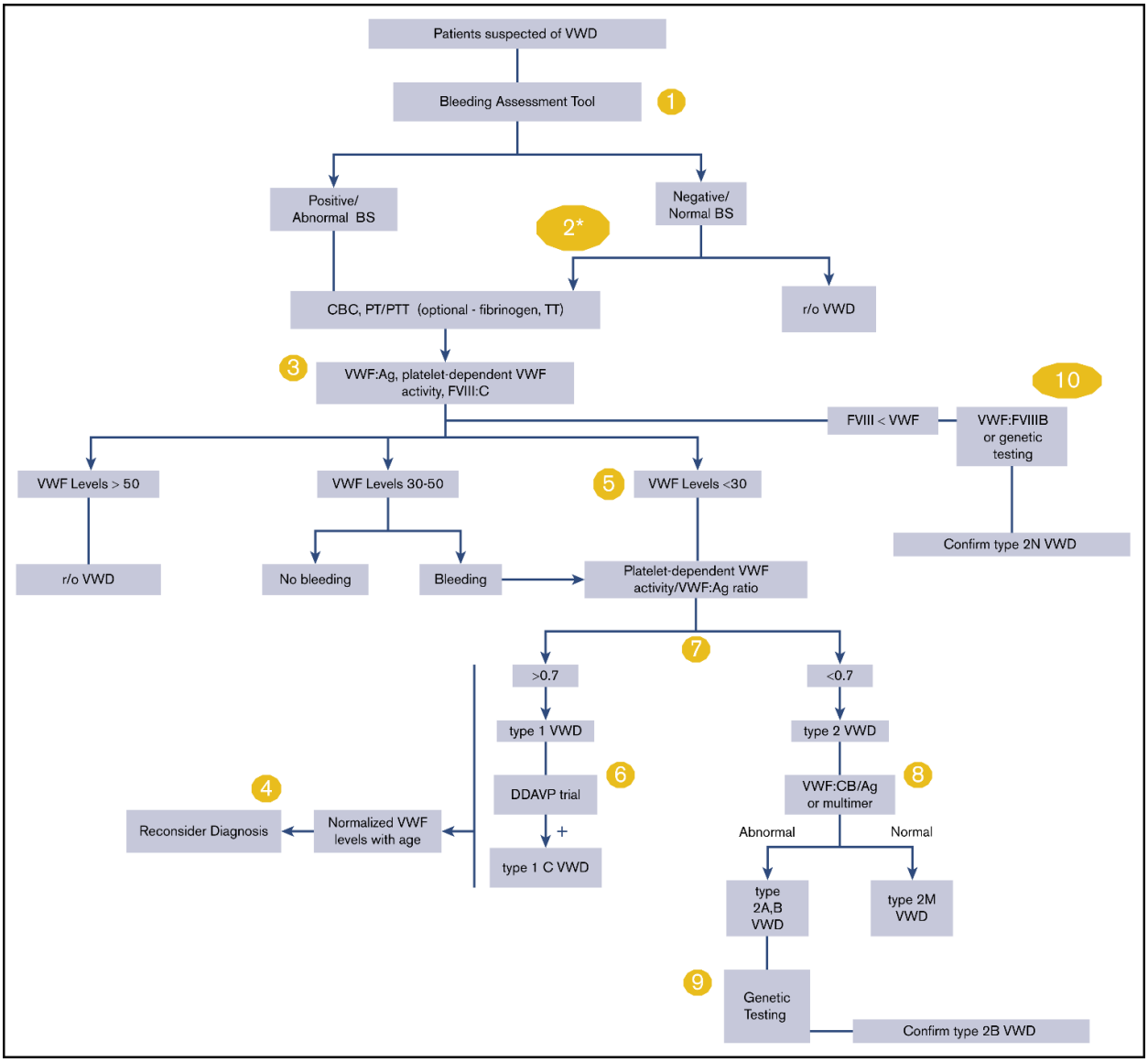
Evaluation for a suspected inherited bleeding disorder involves a thorough documentation of the patient's bleeding history and family history.[2,5,7,8] If the history is suspicious for an inherited bleeding disorder, a platelet count, prothrombin time (PT) test, partial thromboplastin time (aPTT), and fibrinogen test should be the initial screening panel.

Most patients with von Willebrand Disease present with a normal platelet count and coagulation profile.[2] Certain subtypes of von Willebrand Disease are associated with decreased platelet count and the aPTT may be prolonged if FVIII is low.[4,9]

When VWD is suspected based on clinical presentation, guidelines recommend ordering the following quantitative tests: VWF:Ag, VWF activity (several different activity tests are available), and a factor VIII level in order to diagnose VWD and determine the subtype. As VWF is an acute phase reactant, testing should be avoided when other clinical conditions may lead to false positive results. The VWF:Ag determines the total protein VWF level.[4] Von Willebrand activity assesses the functional activity of VWF (usually platelet-binding activity). The historic Ristocetin Cofactor activity assay (VWF:RCo) determines the agglutination of platelets in the presence of the antibiotic ristocetin. Newer functional assays such as VWF:GPIbM, VWF:Ab, and GP1bR, are available to assess VWF activity and have the advantage of being unaffected by common ristocetin binding polymorphisms.[10] In order to diagnose Type 1 VWD, the most common subtype of VWD, the aforementioned testing is often sufficient. The less common subtypes, however, may require additional testing such as VWF multimeric analysis by gel electrophoresis.[4]

Following is an overall sample algorithm addressing the diagnosis of VWD testing. The flowchart was published in *Blood Advances,* and incorporates testing guidelines.[11] It is recommended that each institution adapts their algorithm as practicable.

AN OVERALL ALGORITHM ADDRESSING THE DIAGNOSIS OF VWD [11]



Abbeviations: BS, bleeding score; CBC, complete blood count; DDAVP, desmopressin; FVIII, factor FVIII; FVIII:C, FVIII coagulant activity; PT, prothrombin time; PTT, partial thromboplastin time; r/o, rule out; TT, thrombin time; VWF:CB/Ag, ratio of VWF collagen binding to antigen; VWF:FVIIIB, VWF FVIII binding.PT, prothrombin Time; PTT, partial thromboplastin time; VWD, Von Willebrand disease.

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doi: https://doi.org/10.1182/bloodadvances.2020003265. American Society of Hematology. [11]

INSIGHTS

Initial testing to determine diagnosis of Von Willebrand Disease should be limited to complete blood count (CBC) with platelet count to rule out quantitative platelet disorders, followed by VWF:Ag and VWF activity, and factor VIII level.[2-4]

1. VWD multimer analysis by gel electrophoresis should not initially be ordered to determine if a patient has vWD.[4]
2. VWD multimer analysis by gel electrophoresis is only necessary to assist in diagnosis if a qualitative subtype of VWD (inherited or acquired) is suspected, in which the ratio reveals a discordant

pattern.[2-4]

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