Von Willebrand Disease

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INTRODUCTION & CLINICAL FEATURES

Von Willebrand Disease (vWD) is the most common hereditary bleeding disorder and affects 1.6-2% of the population. The gene encoding von Willebrand Factor (vWF) is located on chromosome 12 and the resultant protein expresses a number of functional domains which participate in hemostasis. Once synthesized, vWF monomers undergo multimerization; with the largest multimers expressing the greatest hemostatic capacity. VWF multimers are then stored in Weibel Palade bodies in the endothelial cell and in alpha granules of platelets.

The two main roles of vWF include the binding of platelets to subendothelial collagen exposed during vessel injury and functioning as a carrier molecule for Factor VIII. While bound to vWF, Factor VIII is protected from premature degradation. Hence, low FVIII levels may be seen in patients with vWD.

TYPE 1 VON WILLEBRAND DISEASE

Type 1 vWD demonstrates autosomal dominant inheritance albeit with variable penetrance – although an affected family member is expected within each generation, the severity may vary widely in clinical relevance.

The abnormal platelet adhesion seen in vWD may lead to prolonged bleeding following dental extraction (i.e., ≥ 3-4 days) or surgery, spontaneous bruising, and menorrhagia. Approximately 90% of women with vWD experience menorrhagia, and up to 20% of unselected women with menorrhagia may have an underlying bleeding disorder (most commonly vWD).

CLINICAL EVALUATION

A careful personal and family history focusing on bruising and bleeding – particularly that associated with surgical procedures, dental extractions, and menses is the first step. The use of aspirin, NSAIDs, or herbal supplements should be inquired about.

The production of vWF is increased by estrogenic influence; mild Type 1 disease is often transiently corrected as pregnancy progresses. The use of exogenous estrogens such as the combined oral contraceptive pill can also increase levels of vWF and can lead to false-negative laboratory testing.

Additionally, vWF is an acute phase reactant and levels can therefore be elevated during acute illness or inflammatory states. A window of 6-8 weeks following cessation of pregnancy, exogenous estrogens, or acute illness is encouraged prior to testing.

If family and patient history are especially convincing, one may proceed with laboratory testing, especially if surgery is planned.

TESTING

Diagnosis of vWD cannot be made with any single test. Instead, a panel is performed which seeks to assess both the absolute level of vWF and the abnormalities expected with vWF deficiency/dysfunction.

A typical profile will include the aPTT, closure time, FVIII:C, vWF:Ag, vWF:RCoF, Ristocetin Induced Platelet Aggregation (RIPA), vWF multimer analysis, and complete blood count.

Prolongations of the aPTT and closure time (a nonspecific test of platelet function) may be seen in patients with vWD.

The vWF:Ag test determines the absolute concentration of vWF in the circulation. Levels may be borderline or reduced in Type 1 disease.

Reductions of FVIII:C are seen in vWD due to deficient binding and stabilization of FVIII in the circulation due to reduced or dysfunctional vWF.

VWF:RCoF test is a functional assay measuring the ability of patient vWF to aggregate reagent platelets following activation by the antibiotic ristocetin. Results in the 'borderline' range of normal (i.e., within 10 U/mL or so) or lower may be seen in patients with mild Type 1 disease.

Ristocetin, in two different concentrations, is also used in platelet aggregometry. Reduced aggregation with high-dose ristocetin is generally associated with more severe reductions in vWF and may not be sensitive to mild disease. The importance of this test lies in the response to low-dose ristocetin: excessive aggregation is highly suggestive of the Type 2B variant of vWD. Type 2B vWD is the result of a gain of function mutation in vWF which leads to

spontaneous binding of vWF to platelets followed by clearance by the reticuloendothelial system of the platelet-vWF complexes resulting in reduced high-molecular-weight vWF multimers and variably decreased platelet counts. DDAVP would be contraindicated in Type 2B vWD as its administration may worsen thrombocytopenia.

vWF multimer analysis by gel electrophoresis may yield any of the following results:

➢entire array of multimer sizes present in typical amounts (Normal);
➢entire array of multimer sizes are present but in reduced amounts (Types 1, 2N and 2M);
➢more hemostatically active high molecular weight multimers absent (Types 2A and 2B); or
➢all multimeric sizes completely absent (Type 3 vWD).

Multimer analysis is an important part of the diagnosis of vWD; Type 1 disease is indicated by the second scenario.

The diagnosis is made in patients bearing the appropriate clinical history and is supported by borderline or grossly abnormal laboratory results. Informing the laboratory of the patient's clinical history is helpful for test interpretation.

MANAGEMENT

Once the diagnosis is made, an otherwise healthy patient with Type 1 vWD may be asked to undergo a DDAVP challenge test. DDAVP (1-desamino-8-D-arginine vasopressin) is administered either intravenously or intranasally. Testing is drawn before and after a dose of DDAVP and a 2-4 fold rise in vWF:Ag, vWF:RCoF, and FVIII:C levels with correction of the prolonged aPTT and closure times is expected in over 90% of individuals with Type 1 vWD. If a good response is documented, this treatment modality may be prescribed prior to surgery or following injury.

DDAVP is typically administered at a dose of 0.3 micrograms/kilogram in 50 cc of normal saline administered intravenously over 30 minutes prior to first incision or following injury. The peak effect occurs at 30-60 minutes and lasts approximately 8-10 hours. Repeated doses are generally not needed but can be administered at 12-24 hour intervals depending on the type and severity of bleeding. The most common side effects are related to vascular and renal including transient flushing, headache, mild hypotension, and rarely, hyponatremia. Repeated dosing is associated with depletion of intracellular vWF stores and would increase the risk of side effects while diminishing the hemostatic benefit.

If a patient is an inappropriate candidate for DDAVP, either due to insufficient DDAVP response or the presence of certain non-Type 1 vWD variants, then treatment with vWF concentrates may be used. The most commonly used product is Humate P® (CSL Behring). VWF concentrates are plasma-derived, virally inactivated concentrates containing both Factor VIII and vWF. Dosing is typically 25-50 IU/Kg when based on the FVIII content and 40-80 IU/Kg when based on the vWF:RCoF content. Subsequent doses can be administered every 8 hours the first day, then every 12 hours for 1-2 more days. The initial dose typically involves the higher end of the dosing range; subsequent dosing the lower end. Repeated doses are usually not necessary after primary hemostasis is established in the first two days. Decisions regarding additional doses and the benefit of reducing bleeding risk must be balanced with the potential for thrombotic complications which may be seen with high circulating levels of FVIII/vWF. Other risks include flushing, allergic reactions, and the largely theoretical risk of viral transmission.

CONCLUSION

Von Willebrand Disease is generally a mild bleeding disorder leading to mucocutaneous and post-procedural bleeding. A careful bleeding history is the cornerstone of diagnosis and crucial in the interpretation of borderline laboratory results. False negative profiles can be seen during acute illness, pregnancy, or with exogenous estrogen use. DDAVP challenge testing allows for documentation of the laboratory response to this agent and to aid in assessing the need for vWF Concentrates.

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