ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Diagnosis of von Willebrand Disease in People With Type O Blood

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H&O Could you give a brief overview of von Willebrand factor (VWF) and the various subtypes of von Willebrand disease (VWD)?

JCG The VWF protein is a very large plasma protein made up of repeating identical subunits. In normal coagulation, VWF acts as an agent for the adhesion of platelets to an injured blood vessel wall through its binding sites for collagen that is present in the subendothelial layer of blood vessels and its binding sites for platelets. VWF also serves as a carrier of factor VIII and protects factor VIII from rapid clearance from the circulation. Normal plasma contains a spectrum of sizes of VWF, and it is believed that the largest forms of VWF are the ones that are active in promoting adhesion of platelets to injured blood vessels.

Type 1 VWD is a quantitative defect; the VWF molecule that is present functions normally but the amount is too low. This may be the result of a defect in synthesis and/or secretion into plasma, or the VWF protein may be cleared more rapidly from plasma. The severity ranges from mild to severe within type 1 VWD.

Type 2 VWD is caused by a dysfunctional molecule and represents a qualitative defect in VWF. There are reports of many mutations in the VWF gene, but currently, on the basis of pathophysiological characteristics, there are 4 accepted classifications of type 2 VWD. In type 2A VWD, platelets are unable to adhere normally to injured blood vessel walls because the large and intermediate-size multimers of VWF are absent. This is caused by one of 2 abnormalities: there may be a mutation in *VWF* that prevents the molecule from forming large multimers, or there may be a mutation that causes the protein to be cleaved more rapidly once it has been secreted into the circulation. As a result, these patients lack the large forms of VWF. In type 2B VWD, patients are missing the highest-molecular-weight multimers of VWF because of a mutation that causes an increase in the binding of VWF to platelets in the circulation. The platelets adsorb the large VWF multimers and form clumps, and both are cleared from the circulation. As a result, these patients lack the large multimers of VWF and also have low platelet counts. Type 2M VWD is caused by a mutation that prevents the VFW molecule from binding to its receptor on the platelet. As a result, the VWF binds to the injured blood vessel wall but does not bring the platelets to the area of the injured blood vessel. Type 2N VWD is caused by a defect in the VWF molecule that prevents factor VIII from binding to VWF. Factor VIII is therefore cleared more rapidly from plasma, resulting in a phenotype similar to mild hemophilia A.

Type 3 VWD represents the complete absence of VWF, and those patients have a very severe bleeding phenotype caused by low factor VIII in the range of moderate hemophilia A, as well as the absence of VWF.

We have long known that VWF has binding sites for the various types of collagen present in the subendothelium of blood vessels through which it promotes platelet adhesion. The current standard screening evaluation of patients suspected to have VWD includes a measurement of VWF quantity (VWF antigen), VWF platelet binding (VWF ristocetin cofactor), VWF multimer pattern, and factor VIII. Recently, Dr Veronica Flood discovered that some patients had isolated defects in the ability of their VWF to bind to various types of collagen. These patients would be missed by a standard evaluation for VWD. Therefore, in patients with a bleeding history consistent

with VWD who have normal standard VWF assays, a VWF collagen binding defect should be considered.

H&O What is the relationship between blood type and levels of VWF?

JCG ABO blood group antigens are defined by the presence of a particular terminal sugar on a carbohydrate chain attached to red blood cells. VWF and factor VIII also contain these antigenic sugars. People with blood group A, for example, have blood group A antigens on their VWF. People with blood group O have an increased clearance of VWF from plasma, which likely is the reason that people with blood group O have VWF levels that are approximately 25% lower than those of people with non-O blood groups. Several studies have linked low VWF levels to the presence of certain *VWF* mutations and blood group O; people who have both a *VWF* mutation and blood group O have lower VWF levels than people with one or the other.

H&O How does having type O blood affect the diagnosis and treatment of VWD?

JCG There is a lot of confusion about whether or not a person with blood group O who has a VWF level that falls above the range for group O individuals but below the normal range for the entire population should be diagnosed with VWD and treated. However, I do not think that it makes a difference why the VWF level is low. Someone whose low VWF level is related to blood group O has the same risk of bleeding as someone whose level is related to a mutation in *VWF*. To mitigate some of this confusion, coagulation laboratories should use the same reference range to report VWF levels for those with blood type O as they would for anyone else in the population.

To add to the confusion about the diagnosis of VWD in persons with blood group O, there are some investigators who firmly believe that you should not diagnose people with VWD unless they have a VWF gene mutation. In 2008, the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) put together an expert panel to define VWD and delineate its diagnosis and management. After much debate, the expert panel decided to define VWD as a VWF level that is 30 IU/dL (30% of normal) or lower. People with higher levels that are still below the normal range might be diagnosed with low VWF rather than with VWD. What remains to be determined is how much bleeding to expect with each level of VWF, and which patients need to be treated. Clinical bleeding episodes that require treatment can occur in patients with low VWF even if they do not meet the strict criteria for the diagnosis of VWD.

H&O Do you agree with the 30% (30 IU/dL) cutoff for a diagnosis of VWD?

JCG Dr Robert R. Montgomery at our institution has been evaluating this question in his NIH-sponsored multicenter study of people with a diagnosis of type 1 VWD. *(Editor's Note: Also see a discussion of this study on pages 137 to 138.)* When he sequenced the entire VWF gene in these patients, he found that nearly all patients with VWF levels lower than 10% of normal—10 IU/dL—had a sequence variance. The majority of patients (71%) with VWF levels between 11% and 20% of normal had a sequence variance, as did 67% of those with VWF levels between 21% and 30% of normal. More than half of patients (52%) with VWF levels between 31% and 40% of normal also had a sequence variance. Based on these results, Dr Montgomery has suggested that a 40 IU/dL (40%) cutoff level be considered for the diagnosis of VWD rather than 30 IU/dL (30%).

H&O Which patients need to be treated for VWD or low VWF?

JCG The problem is that we do not always know which patients are going to bleed. For example, is someone whose VWF level is 45% of normal at risk for excessive bleeding from a tonsillectomy and in need of treatment, even though the strict criteria for a diagnosis of VWD have not been met?

Another complicating factor is that VWF is an acute-phase reactant, meaning that levels increase with stress and inflammation; pregnant women with VWD usually have normal levels of VWF by the end of pregnancy. Levels of VWF also increase as people age. Therefore, you may find different levels of VWF depending on when you test a person's blood.

When I discuss the diagnosis of VWD with patients, I try to help them understand how gray this area can be, and that things may change for them throughout their life. If they develop rheumatoid arthritis, for example, their VWF levels may go up into the normal range. That does not happen in all of cases, however, so that is another area that requires further study. It is also possible that certain sequence variations in the VWF gene may exist that prevent VWF levels from going up with age, for example.

H&O What recent advances have been made in the diagnosis of VWD?

JCG One advance is the description of the collagen abnormalities, which I described earlier. Another advance is the identification of variations in patients with type 1 VWD.

Some patients have low levels of VWF because they clear VWF rapidly, whereas others have low VWF levels because they fail to synthesize or secrete VWF levels normally. Many type 1 VWD patients are treated with desmopressin, a vasopressin analogue that promotes release of VWF and factor VIII from storage sites into the circulation. Whether patients clear their VWF rapidly is an important distinction when treating with desmopressin.

Many patients with type 1 VWD have an excellent response to desmopressin. Their VWF levels go up into the normal range, so we do not have to replace the VWF with agents such as plasma-derived products. Desmopressin often can be used in patients with VWD that is caused by poor synthesis or secretion of VWF, even for surgery, because the molecule functions normally in these patients and has a normal half-life in the circulation. Desmopressin is not as effective in patients with type 1 VWD that is caused by abnormal clearance of VWF, since the VWF is cleared too rapidly to sustain VWF levels in the hemostatic range. Most patients with type 1C VWD, in which the VWF has reduced survival in plasma, will require replacement therapy with a concentrate that contains normal VWF if undergoing surgery or for treatment of major bleeding that requires prolonged therapy.

Another recent advance is the development of a recombinant genetically engineered VWF concentrate that is now in clinical trials. Eventually we should be able to administer this type of product rather than having to rely on plasma-derived products for those who require replacement therapy for treatment of VWD.

Suggested Readings

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