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Low VWF: an established mild bleeding disorder?

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In this issue of *Blood*, Lavin et al report their study of 126 patients who presented at the Irish Reference Center for Bleeding Disorders with bleeding symptoms and von Willebrand factor (VWF) levels between 30 and 50 IU/dL, often referred to as "low VWF."[1]

Their aim was to study the relationship between VWF levels and bleeding phenotype, the laboratory phenotype, and the genetic background of low VWF. All patients underwent a full panel of VWF tests, including VWF activity (VWF:RCo and VWF:CB), VWF antigen (VWF:Ag), VWF propeptide, factor VIII (FVIII:C), and multimer analysis, as well as sequencing of the *VWF* gene and a desmopressin (1-desamino-8-D-arginine vasopressin [DDAVP]) test. The bleeding scores were high for most patients (and very high for some patients) and did not correlate with the level of VWF within the studied range. In addition, the authors found that the reduced VWF levels were caused, in most patients, by decreased synthesis rather than enhanced clearance. Treatment with DDAVP was successful and sustained in the majority of patients with low VWF. These are important findings because these individuals, who are frequently seen in hematology outpatient clinics, pose a significant dilemma with regard to diagnosis and treatment.

Von Willebrand disease (VWD) is caused by a reduction in the concentration and/or activity of VWF and is characterized mainly by mucosal bleeding.[2] Type 1 VWD is diagnosed in patients who have reduced VWF activity (VWF Ristocetin cofactor [VWF:RCo]) and antigen (VWF:Ag) with a VWF:RCo to VWF:Ag ratio >0.6. Type 2 VWD is caused by functional defects in VWF, often reflected by a disproportionately low VWF:RCo (VWF:RCo to VWF:Ag ratio ≤0.6). In type 3 VWD, VWF is absent from the circulation. Diagnosing types 2 and 3 VWD is mostly straightforward, but diagnosing type 1 VWD can be challenging. For many years, there has been debate regarding which cutoff levels of VWF should be used for the diagnosis of VWD. Some use the lower limit of normal (mean – 2 standard deviations of the normal population, which is mostly 50 or 60 IU/dL), others use 40 IU/dL, and in the United Kingdom and United States 30 IU/dL is used as a cutoff value for diagnosing VWD.[3–5] Previously, moderately reduced VWF levels (30-50 IU/dL) were considered a risk factor for bleeding rather than a true bleeding disorder, and this group is referred to as low VWF.[6] However, this poses difficulties for physicians who do not have a clear indication of whether or not to treat these individuals and for patients who do not know whether they have a bleeding disorder. In a recent study by Flood et al,[7] historically diagnosed VWD patients with VWF levels higher than 30 IU/dL also had high bleeding scores based on the well-known mucocutaneous bleeding phenotype of type 1 VWD. However, that study included patients with a previous diagnosis of VWD, and diagnostic VWF levels did not have to meet specific criteria for study inclusion.

In the first ever study by Lavin et al that investigated clearly defined low VWF patients in detail, the results may indicate that individuals with moderately reduced VWF levels should be considered as having a mild bleeding disorder, for which DDAVP is a good treatment option. Importantly, the reduced VWF levels seem to be the cause for the bleeding phenotype, because after extensive evaluation (mild) coagulation defects were found in only 10 of 91 patients with a high bleeding score. Although disorders in fibrinolysis were not included in the evaluation, these disorders are very rare and do not seem to play a role in determining the bleeding phenotype in VWD.[8] On the basis of the distribution of VWF levels in the general population, there are many more individuals with low VWF levels who never bleed. Future research that compares low VWF patients with individuals who have low VWF levels but do not bleed is needed to identify possible explanations.

The study by Lavin et al also provides further insight into the poorly understood pathophysiology of low VWF. A probably damaging *VWF* gene variant was found in only 40% of patients, a percentage similar to that reported by Flood et al.[7] Therefore other factors outside the *VWF* gene likely play a role. The high FVIII:C to VWF:Ag ratio in this study points toward a defect in VWF production and/or secretion, the exact mechanism for which needs to be investigated.

Some issues still remain. One such issue is the age-related increase in VWF levels, which was almost 2 IU/dL per year in the Lavin et al study; in 29 individuals, this led to normalization of VWF levels. It is not known whether normalization of historically low VWF levels also normalizes the bleeding phenotype, and thus it is not known if we should or should not treat patients with normalized VWF levels. The only study performed to date showed that elderly individuals with type 1 VWD still have bleeding incidence rates similar to those of younger individuals despite their higher VWF levels.[9] Another open issue is the bleeding risk in individuals with low VWF when they undergo surgery or interventions. Although this study[1] shows that VWF levels rise adequately after DDAVP, the need for and effectiveness of DDAVP during surgery must be determined. These questions will require prospective studies in low VWF patients.

The study by Lavin et al underlines the importance of low VWF. It suggests that patients with bleeding symptoms who are diagnosed with low VWF should be seen as having a mild bleeding disorder rather than having a risk factor for bleeding.

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REFERENCES

1. Lavin M, Aguila S, Schneppenheim S, et al. Novel insights into the clinical phenotype and pathophysiology underlying low VWF levels. *Blood*. 2017;130(21):2344-2353.

2. Leebeek FW, Eikenboom JC. Von Willebrand's Disease. *N Engl J Med*. 2016;375(21):2067-2080.

3. Castaman G, Goodeve A, Eikenboom J; European Group on von Willebrand Disease. Principles of care for the diagnosis and treatment of von Willebrand disease. *Haematologica*. 2013;98(5):667-674.

4. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia*. 2008;14(2):171-232.

5. Laffan MA, Lester W, O'Donnell JS, et al. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *Br J Haematol*. 2014;167(4):453-465.

6. Sadler JE. Von Willebrand disease type 1: a diagnosis in search of a disease. *Blood*. 2003;101(6):2089-2093.

7. Flood VH, Christopherson PA, Gill JC, et al. Clinical and laboratory variability in a cohort of patients diagnosed with type 1 VWD in the United States. *Blood*. 2016;127(20):2481-2488.

8. De Wee EM, Klaij K, Eikenboom HC, et al; WiN Study Group. Effect of fibrinolysis on bleeding phenotype in moderate and severe von Willebrand disease. *Haemophilia*. 2012;18(3):444-451.

9. Sanders YV, Giezenaar MA, Laros-van Gorkom BA, et al; WiN study group. von Willebrand disease and aging: an evolving phenotype. *J Thromb Haemost*. 2014;12(7):1066-1075.

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