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FORUM

Von Willebrand disease diagnosis: from complexity to simplicity

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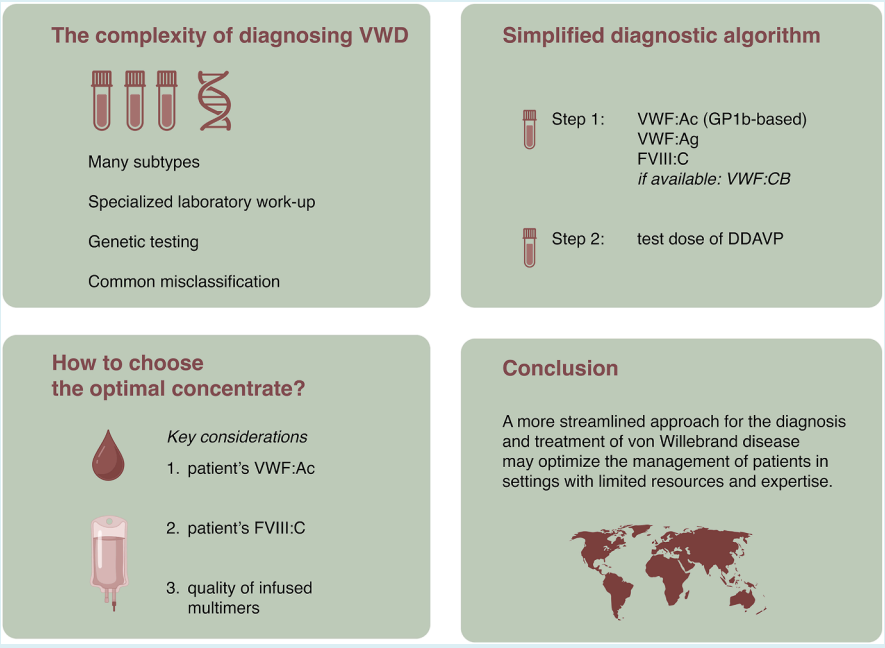
Abstract

Von Willebrand disease (VWD) is a complex disorder in terms of both its pathophysiology and treatment. The broad recognition and treatment of patients with VWD is often hindered by the complicated diagnostic process. Therefore, a more streamlined approach is needed, particularly in settings with limited expertise or resources. One practical initial strategy is to prioritize measuring von Willebrand factor (VWF) activity using a robust assay, alongside VWF antigen and factor (F)VIII levels, and administering a test dose of desmopressin. Once a diagnosis has been established, 3 variables should be considered for patients requiring replacement therapy: the patient's endogenous VWF activity and FVIII levels, and the quality of the infused multimers, as reflected by the VWF activity/antigen ratio of the concentrate. This simplified framework can facilitate the global diagnosis and management of VWD patients. However, we acknowledge the limitations, particularly with regard to accurately subtyping patients with type 2 VWD, since precise classification is essential for optimal care.



KEYWORDS
diagnosis, factor VIII, multimeric proteins, Von Willebrand diseases, von Willebrand factor

Essentials

- The complexity of diagnosing von Willebrand disease hinders the recognition of new patients.
- Focusing on von Willebrand factor (VWF) and FVIII levels may simplify the diagnosis.
- Factor choice depends on VWF activity, FVIII and the quality of the infused VWF multimers.
- A streamlined diagnostic approach may optimize the global management of von Willebrand disease.

1 | INTRODUCTION

Von Willebrand factor (VWF) plays a unique role in blood clot formation. It is essential for primary haemostasis and is also involved in blood coagulation. VWF relies on its multimeric structure to fulfill two of its physiological roles [1]: platelet adhesion to the vessel wall and platelet aggregation, while binding and protection of factor (F) VIII can be provided by the smallest VWF subunits. These diverse functional properties underlie the wide range of clinical manifestations [2], the existence of multiple disease types and subtypes, and the diagnostic and therapeutic complexity of von Willebrand disease (VWD). Treating VWD requires correcting both primary haemostasis and FVIII deficiency, if present. In the past decades, we have witnessed an increase in the understanding of VWD and the therapeutic options [3].

However, despite being the most prevalent inherited bleeding disorder, VWD remains underdiagnosed today [4–7]. This is particularly evident in lower-middle-income and lower-income countries, where patient registration rates are significantly lower [8]. Furthermore, female patients are underrepresented in several regions of the world. Reasons for the misrecognition of VWD include a lack of awareness in the clinic, a lack of specialized laboratories and diagnostic tools, the cost of reagents, the presence of preanalytical [9], analytical, and postanalytical issues, and the underuse of validated bleeding assessment tools. These difficulties are in part aggravated by the current complexity of establishing a VWD diagnosis. In order to improve the recognition of patients with VWD, it appears necessary to simplify its diagnosis and management.

2 | THE COMPLEXITY OF DIAGNOSING VWD

The diagnosis of VWD has become increasingly complex due to the numerous subtypes and the reliance on specialized assays that are not readily available in many laboratories. Measuring VWF antigen (VWF:Ag) levels helps to identify a quantitative deficiency and differentiate between partial (type 1) and complete deficiencies (type 3) [3]. By contrast, type 2 VWD is characterized by a functional defect in VWF. The most commonly used functional assays assess the ability of VWF multimers to aggregate platelets in the presence of ristocetin (ristocetin cofactor activity), to bind to the glycoprotein 1b (GP1b) receptor, or to interact with collagen. The first-line tests, ie, VWF:Ag, platelet-dependent VWF:Activity (VWF:Ac) and FVIII:C, can reliably exclude VWD, and distinguish type 1 from type 3 VWD. However, further subtyping of type 2 VWD requires additional testing including VWF collagen-binding (VWF:CB), VWF-FVIII binding (VWF:FVIIIB) and ristocetin-induced platelet aggregation (RIPA) assays. Although not specifically addressed in the current guidelines [10], the most relevant first-line test is the measurement of VWF activity, which is decreased in all types and subtypes of VWD except type 2N.

Type 2B VWD, typically characterized by reduced VWF activity, can be suspected in case of thrombocytopenia. However, a study by Federici et al. found that 24% of patients with type 2B VWD had a normal platelet count at baseline and under stress conditions, including administration of deamino D-arginine vasopressin (DDAVP) [11]. In the Dutch WiN cohort, thrombocytopenia was present in only 67.2% of patients with type 2B VWD [12]. The diagnosis of type 2B VWD is confirmed by a RIPA assay [3]. Furthermore, genetic testing is required to distinguish type 2B VWD from platelet-type VWD, where a hyperactive platelet GPIbα receptor also results in an enhanced RIPA assay. This distinction is important for therapeutic purposes, as platelet transfusions are preferred in cases of platelet-type VWD [13]. The presence of low factor VIII levels in the absence of VWF deficiency, as detected by routine quantitative or qualitative assays, may suggest type 2N VWD or mild haemophilia A. These conditions, which differ in their inheritance patterns, can be distinguished using the VWF:FVIIIB binding assay and confirmatory genetic testing.

Confirming subtypes 2A or 2M requires multimeric analysis and/or genetic testing, which may not be available in all clinical settings. The VWF:CB assay can serve as an alternative to multimer analysis. Moreover, interpretation of genetic variants is not always straightforward because of frequent benign variants in VWF and the influence of other genes than VWF on the plasma levels of VWF [14]. Furthermore, a 2M/A overlap subtype has recently been proposed [15], exhibiting features of both type 2M and type 2A. Also, misclassification is common, as many patients initially diagnosed with type 2M have been reclassified as having type 1 VWD [16].

Recently, Federici proposed simplifying the diagnostic process in Italy by using the VWF:CB assay alongside the 3 first-line assays: VWF:Ag, GP1b-based VWF:Ac and FVIII:C [17]. This approach incorporates the administration of DDAVP, with the 4 different assays being measured at timepoint zero and after 1 and 4 hours. This enables conditions involving enhanced clearance of VWF, such as type 1 VWD Vicenza and acquired von Willebrand syndrome, to be diagnosed. DDAVP is an inexpensive and widely available treatment option for patients with VWD. This approach also has the advantage of identifying patients who may benefit from DDAVP treatment. In summary, combining first-line VWF assays (including VWF:CB, if possible) with a test dose of DDAVP constitutes an appealing diagnostic algorithm for countries with limited resources. However, if more specialized assays and genetic testing are available, a full work-up remains the preferred option, as some patients may be misdiagnosed.

3 | THE PRACTICAL MANAGEMENT OF VWD REVISITED

The objective of treating VWD is to achieve and maintain haemostatic levels of VWF and FVIII. In many cases DDAVP cannot be used, and VWF factor supplementation is needed. In clinical practice, 3 variables should, in our view, be taken into account when using clotting factor concentrates in VWD: the patient's VWF activity as measured by a robust assay, the patient's endogenous FVIII level, and the quality of the infused VWF multimers.

First, the decrease in VWF activity—whether primary, as in qualitative defects, or secondary, as in quantitative deficiencies—is a key determinant of the bleeding phenotype in patients with VWD. To have a good estimate of the VWF activity, a performant platelet-dependent assay should be used. Newer assays such as the GP1b-binding assay (VWF:GP1bM or VWF:GP1bR) are recommended over the traditional ristocetin cofactor activity assay [10]. These newer assays are more accurate, because VWF:RCo exhibits high assay variability and poor sensitivity to VWF at low levels [18]. Moreover, it may produce false low activity levels when the common A1 domain polymorphism D1472H is present [19]. This polymorphism is found in 63% of African-American individuals and 17% of White individuals. It should be noted that the VWF:GPIbR assay, which uses ristocetin to induce binding of VWF to a wild-type GPIb fragment, is unaffected by this polymorphism [20].

When choosing a VWF concentrate, careful consideration should be given to its reported VWF activity, as this reflects the quality of the multimers it contains and their capacity to correct the specific qualitative or quantitative defect identified in the patient.

In some patients with VWD, bleeding symptoms are due not only to reduced VWF levels, but also to a concomitant decrease in FVIII levels. This dual deficiency is particulary important to understand the soft tissue bleeding tendency in VWD. In contrast to the FVIII decrease in mild haemophilia A, the production and secretion of FVIII is preserved in VWD patients [21]. Therefore, it is important to consider the baseline FVIII activity, which can vary between patients, in choosing the optimal supplementation to avoid the thrombotic risk that is associated with supraphysiological FVIII levels [22]. Interestingly, patients with subtype 2N, which is characterized by an isolated defect in FVIII binding and protection, often present with soft tissue bleeding similar to a mild haemophilia phenotype. As such, a few case reports highlighted the successful use of FVIII supplementation in the perioperative management of type 2N VWD patients [23,24]. However, mucocutaneous bleeding symptoms are also frequently reported, which can be attributed to underlying genetic heterogeneity, with some patients having a null mutation that leads to decreased VWF levels [25]. Thus, most patients require supplementation of functional VWF alongside FVIII for optimal bleeding control. Therefore, discriminating between type 2N VWD and mild haemophilia, using genetic testing or the specialized VWF:FVIIIB, remains crucial for its proper management. This is exemplified by case reports where a simplified approach has resulted in mismanagement [26,27].

Finally, the distribution of VWF multimers in plasma-derived concentrates is important for both their therapeutic efficacy and safety. Ideally, they should contain a high proportion of high-molecular-weight multimers, since these multimers perform most of VWF's functions. Short multimers and monomers only aid in the protection of FVIII, which is only relevant in VWD patients with secondary FVIII deficiency. This principle is exemplified by the design of efanosoctocog alpha. Attaching the D-D' domain of VWF to the recombinant FVIII molecule is sufficient to prolong its half-life, enabling weekly infusion [28].

The available plasma-derived concentrates differ in terms of their VWF content, the functional integrity of their multimers, and their FVIII quantities. A commonly used metric is the ratio of VWF:Ac to FVIII activity (VWF:Ac/FVIII). This ratio varies significantly between products, ranging from <1 (eg, Alphanate and Factor 8Y), to around 1 (eg, Fanhdi, Immunate, and Wilate), to close to 2 (eg, Haemate P). Wilfactin, a product with a high ratio, contains < 10 IU of FVIII per 100 IU of VWF:Ac. Paradoxically, intermediate ratio concentrates, containing lower amounts of FVIII relative to VWF, pose a risk of supraphysiological FVIII levels [29]. The long-term accumulation of FVIII is influenced not only by the administration of exogenous FVIII but also by the stabilization and protection of endogenous FVIII by infused VWF. Interestingly, one study found that a 1:1 low ratio VWF/FVIII concentrate did not result in FVIII accumulation over time in the perioperative setting [30]. Postoperative VWF levels after >48 hours were not available though. Similarly, no VWF accumulation was observed with a 1:1 ratio plasma-derived VWF/FVIII concentrate used prophylactically [31]. These trials highlight the need to monitor FVIII and VWF levels postoperatively. However, it is too early to recommend one product over another, as there are no performant pharmacokinetic models, and trials involving a larger number of patients or direct prospective comparisons are lacking.

Another informative ratio is the VWF activity-to-antigen ratio (VWF:Ac/Ag) of the concentrate, ranging from 0.3 (eg, Factor 8Y) to around 0.5 (eg, Alphanate, Fanhdi, Haemate P, and Immunate), and close to 1 (eg, Wilate). A ratio of 1 indicates good multimeric quality

of the VWF present. A ratio <1 suggests the presence of smaller multimers that contribute to antigen quantity but are less functionally effective. If smaller VWF entities (dimers or monomers) or degraded multimers predominate, they may protect endogenous FVIII, but they will not ensure effective primary haemostasis. Thus, attention should be given to the quality and stability of the VWF multimers administered to each patient, as well as to their long-term stability after administration.

4 | CONCLUSION

In conclusion, the complex diagnosis of VWD hampers the widespread recognition of patients and their management. Therefore, a more concise diagnostic approach, prioritizing the VWF:Ac using a robust assay, the VWF:Ag and FVIII levels, in combination with a test dose of DDAVP, may be advantageous in low-income countries and settings where VWD expertise is limited. In cases where DDAVP is not a treatment option, the optimal clotting factor concentrate should be chosen with three considerations in mind: the patient's VWF activity level, the endogenous FVIII level, and the quality of the infused multimers. Using this streamlined diagnostic and therapeutic approach, the global management of von Willebrand patients could be optimized in settings with limited resources and expertise. However, limitations remain when it comes to accurately subtyping VWD and subsequently determining the most suitable treatment approach.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE

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