Von Willebrand Disease

Jonathan Leroy [a], Pierre Péters [b], Laurence Dedeken [c], Laure Kornreich [c], Phu Quoc Le [c]

[a] Department of Paediatrics, Hôpital Civil Marie Curie, U.L.B., Charleroi, Belgium
[b] Biological Haematology department, Centre Hospitalier Universitaire de Liège, Liège Belgium
[c] Department of Haematology-Oncology, Hôpital Universitaire des Enfants Reine Fabiola, H.U.B, U.L.B., Brussels, Belgium

jonathan.leroy@humani.be

Keywords
von Willebrand Factor ; von Willebrand Disease ; Haemostasis ; Quality of Life

Abstract
Von Willebrand disease (VWD) is the most common inherited bleeding disorder, caused by quantitative or qualitative defects of von Willebrand factor (VWF). This multimeric glycoprotein plays a central role in haemostasis by binding to extracellular matrix proteins such as collagen and to platelets via the glycoprotein Ib receptor. In addition, VWF acts as a carrier for factor VIII, preventing its premature clearance and degradation. Defective VWF function results in a bleeding tendency, predominantly manifesting as mucocutaneous haemorrhages (epistaxis, easy bruising, gum bleeding, and menorrhagia). The severity of symptoms varies not only between patients but also over time in the same individual, leading to a significant impact on quality of life. Diagnosis relies on the evaluation of bleeding history, family history, and specialized laboratory assays, yet it often remains challenging despite recent advances.

Introduction

Von Willebrand disease (VWD) affects approximately 1% of the general population, though clinically significant bleeding occurs in about 1 in 1000 individuals. Its prevalence is consistent across different races and ethnicities. Unlike haemophilia, VWD is transmitted in an autosomal manner, affecting both men and women. However, due to menstruation, pregnancy, and childbirth, women experience a disproportionate clinical burden (1-4).

The disorder is caused by either quantitative or qualitative deficiencies in VWF and is classified into three main types: type 1, 2 (with subtypes 2A, 2B, 2M, and 2N), and 3. Type 1 is the most frequent, involving partial deficiency; type 3 represents complete absence of VWF; and type 2 includes functional abnormalities. While type 1 predominates, diagnostic thresholds - particularly in cases with borderline VWF levels (30–50 IU/dL, historically termed "low VWF") - remain debated. Diagnosis should integrate clinical phenotype and family history alongside laboratory results (4,5).

Classification

Most cases of VWD are inherited in an autosomal dominant manner, while type 3 and type 2N follow autosomal recessive inheritance. Type 1 accounts for 70–80% of cases, type 2 for about 20%, and type 3 for less than 5% (6,7).

- Type 1: Partial quantitative deficiency of VWF. A subtype, type 1C, involves increased VWF clearance.
- Type 3: Complete absence of VWF, leading to severe bleeding.
- Type 2: Qualitative abnormalities, subdivided as follows:
  - 2A: Defective VWF multimerization.
  - 2B: Increased affinity for GPIb.
  - 2M: Defective binding despite normal multimer structure.
  - 2N: Impaired FVIII binding, mimicking haemophilia A.

Historically, patients with VWF levels between 30–50 IU/dL were categorized as "low VWF". However, many experience clinically significant bleeding, warranting individualized management. According to 2021 guidelines, a diagnosis of type 1 VWD is supported when VWF levels are ≤30 IU/dL, regardless of bleeding history, or ≤50 IU/dL in the presence of abnormal bleeding (5). Table 1 summarizes the different subtypes of VWD and their characteristics.

Clinical Characteristics

VWD typically presents with mucocutaneous bleeding, including recurrent epistaxis, oral cavity bleeding, easy bruising, and menorrhagia. Gastrointestinal bleeding - often linked to angiodysplasia - is a difficult-to-treat complication, especially in elderly patients and those with type 2A or type 3 disease (8-9).

Bleeding may also occur after surgery, trauma, or childbirth. Hemarthroses and deep muscle bleeds are rare, usually confined to type 3 VWD. Spontaneous bleeding is uncommon even in severe deficiency. Women are more symptomatic due to menstrual and obstetric challenges. The phenotype often fluctuates over a patient's lifetime, requiring individualized diagnosis and management (4,10).

Diagnosis

Diagnosis relies on three elements: a personal bleeding history often obtained through the application of a bleeding assessment tools (BATs), specialized laboratory findings consistent with reduced levels and/or dysfunction of VWF, and family history.

Assessment of bleeding phenotype

BATs are increasingly used to quantify bleeding severity. The 2021 guidelines recommend validated BATs for screening, especially in women, before proceeding to laboratory testing. However, some limitations appear when using these tests with young people without any bleeding challenges to overcome (11).

Laboratory Evaluation

Complete blood count, activated partial thromboplastin time (aPTT) and prothrombin time are usually normal, though aPTT may be prolonged in severe cases and platelets may be variably lower in type 2B disease. Initial diagnostic tests include (12-14):

- VWF antigen (VWF:Ag)
- VWF platelet-dependent activity (VWF:Act)
- Factor VIII activity (FVIII:C)

Both quantitative and functional assays are required for accurate classification. The VWF activity-to-antigen ratio is used to differentiate between quantitative vs qualitative deficiency of VWF (VWD type 1 vs type 2), with type 2 characterized by an activity/antigen ratio <0.7. Multiple assessments are often necessary, as VWF levels fluctuate with age, stress, inflammation, blood group (lower in type O), pregnancy, and hormonal factors (15).

Furthermore, VWF multimer analysis helps distinguish the patient's subtype of VWD. In types 1, 2M, and 2N VWD, all sizes of multimers are seen, while preferential loss of high-molecular-weight multimers is seen in type 2A and type 2B. Type 3 VWD is characterized by almost complete absence of VWF multimers (5).

Genetic Testing

Molecular testing can confirm difficult cases, differentiate subtypes, and guide family planning. It is particularly valuable in distinguishing type 2N VWD from mild haemophilia A, type 2B from platelet-type VWD, and congenital from acquired forms (16).

Treatment

Therapeutic strategies are generally safe and effective when guided by specialist care. Management involves antifibrinolytics, desmopressin, and VWF concentrates, tailored to the type and severity of disease (14,16,17).

- Tranexamic acid: Antifibrinolytic used for mild bleeding and minor procedures. Can be administered topically, orally, intravenously, or subcutaneously.

TABLE 1: Characteristics of the subtypes of VWD

VWB subtype	Inheritance	Pathobiology and Lab testing
Type 1	Autosomal dominant but incomplete penetrance	- Partial quantitative VWF deficiency. - Concordant reductions in VWF:Ag and VWF functional assays. - Includes VWF mutations causing rapid clearance
Type 2A	Mostly autosomal dominant	- Decreased VWF-dependent platelet adhesion. - Discordant reduction in VWF functional assays compared to VWF:Ag levels (ratio VWF:Act/VWF:Ag < 0.7). - Reduction in high-molecular weight (HMW) multimers.
Type 2B	Autosomal dominant	- Increased VWF affinity for platelet Gp1b. - Discordant reduction in VWF functional assays compared to VWF:Ag levels (ratio VWF:Act/VWF:Ag < 0.7). - May be associated with loss of HMW multimers ± thrombocytopenia.
Type 2M	Autosomal dominant	- Decreased VWF-dependent platelet adhesion. - Discordant reduction in VWF functional assays compared to VWF:Ag levels (ratio VWF:Act/VWF:Ag < 0.7). - Normal multimers. - Diagnosis by exclusion.
Type 2N	Autosomal recessive	- Decreased VWF binding affinity for FVIII. - Reduced FVIII:C levels (ratio FVIII:C/VWF:Ag < 0.7). - Plasma VWF:Ag often normal or slightly reduced.
Type 3	Autosomal recessive	- Severe quantitative VWF deficiency. - Plasma VWF:Ag < 5 IU/dL.

- Desmopressin (DDAVP): Stimulates release of endogenous VWF and FVIII. Effective in many type 1 and select type 2 cases, but contraindicated in type 2B and ineffective in type 3. However, this can only be used after a challenge test and not before the age of 2-3 years.
- VWF concentrates: Indicated for patients unresponsive to DDAVP or with severe disease (type 2B, type 3). May also be indicated in patients responsive to DDAVP undergoing major surgery.
- Hormonal and iron therapy: Used for menorrhagia and to correct anaemia.

Perioperative Management

Careful risk stratification and perioperative planning are essential. Factors include type of surgery, baseline VWF levels, prior haemostatic response, and bleeding history. Tailored dosing of VWF/FVIII substitution is needed and should be prescribed in consultation with the paediatric haematologist.

Emerging Therapies

Recombinant VWF (rVWF) has shown efficacy in clinical trials, though it was not superior to tranexamic acid for heavy menstrual bleeding. The off-label use of Emicizumab, a bispecific monoclonal antibody that mimics FVIII function, in type 3 VWD has shown promising results and is currently being investigated in a trial to confirm its efficacy and safety (18,19).

Conclusion

VWD is associated with significant morbidity due to recurrent mucocutaneous bleeding. Early recognition and individualized treatment are key to minimizing complications and burden. Advances in understanding VWF biology have refined diagnostic and therapeutic strategies, yet challenges persist in ensuring accurate diagnosis and equitable access to effective treatment. Ongoing research into novel therapies remains essential to address unmet needs in this patient population.

Statement

The authors have no conflicts of interest relating to the topic discussed in this manuscript.

REFERENCES

1. Bowman M, Hopman W.M, Rapson D, Lillicrap D and James P. The prevalence of symp- tomatic von Willebrand disease in primary care practice. J Thromb Haemost. 2010;8(1):213-216.
2. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood 1987; 69(2): 454–459. pmid:3492222
3. Sadler JE, Mannucci PM, Berntorp E, Bochkov N, Boulyjenkov V, Ginsburg D, et al. Impact, diagnosis and treatment of von Willebrand disease. Thromb Haemost. 2000,84:160–174.
4. Brignardello-Petersen R, El Alayli A, Husainat N, Kalot MA, Shahid S, Aljabirii Y et al. Gynecologic and obstetric management of women with von Willebrand disease: summary of systematic reviews of the literature. Blood Adv 2022; 6(1):228–237.
5. James PD, Connell NT, Ameer B, Di Paola J, Eikenboom J, Giraud N, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. Blood Adv. 2021;5:280–300.
6. Leebeek FW, Eikenboom JC. Von Willebrand's Disease. N Engl J Med. 2016 Nov 24;375(21):2067–2080
7. Sadler JE, Budde U, Eikenboom JCJ, Favaloro EJ, Hill FGH, Holmberg L, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost. 2006;4:2103-2114.
8. de Wee EM, Sanders YV, Mauser-Bunschoten EP, van der Bom JG, Degenaar-Dujardin ME, Eikenboom J, et al. Determinants of bleeding phenotype in adult patients with moderate or severe von Willebrand disease. Thromb Haemost, 2012 ;108, 683–692.
9. Makris M, Federici AB, Mannucci PM, Bolton-Maggs PHB, Yee TT, Abshire T et al. The natural history of occult or angiodysplastic gastrointestinal bleeding in von Willebrand disease. Haemophilia 2015; 21(3):338–342.
10. van Galen KP, Mauser-Bunschoten EP, Leebeek FW. Hemophilic arthropathy in patients with von Willebrand disease. Blood Rev 2012; 26(6):261–266.
11. Kalot MA, Husainat N, Tayiem S, El Alayli A, Dimassi AB, Diab O, et al. Bleeding assessment tools in the diagnosis of VWD in adults and children: a systematic review and meta-analysis of test accuracy. Blood Adv. 2021;5:5023–31.
12. Favaloro EJ, Pasalic L, Curnow J. Laboratory tests used to help diagnose von Willebrand disease: an update. Pathology. 2016;48:303-318.
13. Sharma R, Haberichter SL. New advances in the diagnosis of von Willebrand disease. Hematology Am Soc Hematol Educ Program. 2019;2019:596–600.
14. Laffan MA, Lester W, O'Donnell JS, Will A, Campbell Tait R, Goodeve A, 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;167:453-465
15. Abou-Ismail MY, James PD, Flood VH, Connell NT. Beyond the guidelines: how we approach challenging scenarios in the diagnosis and management of von Willebrand disease. J Thromb Haemost. 2023;21(2):204- 214.
16. James P, Leebeek F, Casari C, Lillicrap D. Diagnosis and treatment of von Willebrand disease in 2024 and beyond. Haemophilia. 2024;30(Suppl. 3):103–111.
17. Connell NT, Flood VH, Brignardello-Petersen R, Abdul-Kadir R, Arapshian A, Couper S, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Blood Adv. 2021;5(1):301-325.
18. Ragni MV, Rothenberger SD, Feldman R, Nance D, Leavitt AD, Malec L,et al. Recombinant von Willebrand factor and tranexamic acid for heavy menstrual bleeding in patients with mild and moderate von Willebrand disease in the USA (VWDMin): a phase 3, open-label, randomised, crossover trial. Lancet Haematol. 2023;3026(23):1-12.
19. Shanmukhaiah C, Jijina F, Kannan S, Pai NG, Kulkarni B, Khuba SV, et al. Efficacy of emicizumab in von Willebrand disease (VWD) patients with and without alloantibodies to von Willebrand factor (VWF): report of two cases and review of literature. Haemophilia. 2022;28(2):286-291.