



DISORDINI EMORRAGICI CONGENITI: ASPETTI
DIAGNOSTICI E CLINICI

FROM VON WILLEBRAND DISEASE TO MILD HEMOPHILIA A AND BACK: THREE ILLUSTRATIVE CASES HIGHLIGHTING THE ROLE OF GENETIC TESTING IN IMPROVING DIAGNOSTIC ACCURACY

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Background. von Willebrand disease (VWD) is an inherited bleeding disorder caused by quantitative or qualitative defects of von Willebrand factor (VWF), often associated with reduced factor VIII (FVIII). Clinical presentation mainly involves mucocutaneous bleeding; VWF activity between 30–50 UI/dl can be classified as “low VWF”. Inheritance is autosomal dominant or recessive, depending on subtype. Hemophilia A is an X-linked disorder due to FVIII deficiency; mild forms (FVIII activity 5–40 UI/dl) often present after trauma or surgery. Differential diagnosis between mild hemophilia A and VWD may be challenging, with implications for management and genetic counseling. Genetic testing is not routinely performed in all VWD subtypes but can be useful in selected cases.

Case report. Case 1: a 36-year-old woman was referred during pregnancy for prolonged aPTT. At 16 gestational weeks, FVIII (chromogenic assay) was 49 UI/dl, VWF activity (GP1bM) 69 UI/dl; she reported easy bruising and menorrhagia. Her father had a bleeding history and a reported (undocumented) VWD diagnosis. Postpartum exams showed persistently reduced FVIII (34 UI/dl) with mildly decreased VWF activity and antigen (44 and 51 UI/dl). Genetic analysis included next generation sequencing (NGS) of VWF and F8, with exonic deletion/duplication analysis, intron 22 and 1 inversion screening, F8 promoter Sanger sequencing. No pathogenic VWF variants were identified, while a heterozygous F8 promoter c.-257T>G variant, associated with mild hemophilia A, was detected. The variant was confirmed in her father and son (FVIII 43 and 18 UI/dl, normal VWF in both); an obligate carrier sister had FVIII 44UI/dl, normal VWF. X-inactivation in the proband was not markedly

skewed. Case 2: a 70-year-old man was referred for re-assessment of bleeding risk and management in atrial fibrillation. He was diagnosed with VWD at age 40 based on VWF activity 28–36 UI/dl and post-procedural bleeding. Current evaluation showed normal VWF (activity 94UI/dl, antigen 125 UI/dl) but persistently reduced FVIII (29–36 UI/dl). Genetic testing identified no VWF variants and a hemizygous F8 promoter c.-219C>T variant, causative of mild hemophilia A. He underwent left atrial appendage closure and anticoagulation (dabigatran) with prophylaxis using pegylated recombinant FVIII. His daughter, obligate carrier, had FVIII 57.6 UI/dl and no bleeding phenotype. Case 3: a 20-year-old man was diagnosed with mild hemophilia A based on reduced FVIII activity (25–37 UI/dl) and normal VWF, after prolonged aPTT during presurgical screening, without personal or familial bleeding history. F8 testing was negative, while the homozygous VWF c.2561G>A (p.Arg854Gln) pathogenic variant, associated with autosomal recessive type 2N VWD, was identified, leading to diagnostic reclassification.

Conclusions. genetic testing enabled diagnostic reclassification, with relevant implications for clinical management and genetic counseling. In case 1, mildly reduced VWF suggests possible coexisting low VWF, consistent with evidence that up to 50% of such cases lack identifiable variants, potentially contributing to her low FVIII levels, not fully explained by X-inactivation. Notably, F8 promoter variants are not routinely covered by standard NGS panels, underscoring the importance of targeted analysis in specialized centers. Although still not routinely performed, genetic testing may be decisive in patients with atypical or discordant phenotypes.