The diagnosis of Von Willebrand disease

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Von Willebrand disease (VWD) is the most frequent inherited bleeding disorder and is characterized by a muco-cutaneous bleeding phenotype. The diagnosis of VWD is based on a personal bleeding history and / or a positive family history of bleeding. If VWD is suspected based on the clinical symptoms, laboratory tests should be performed. Three laboratory tests are the mainstay of the diagnosis: VWF antigen (VWF:Ag), VWF ristocetin cofactor activity (VWF:RCo) and FVIII coagulant activity (FVIII:C). Type 3 VWD is diagnosed based on a VWF:Ag of <5 IU/dL. In type 1 VWD, the most frequently occurring type of VWD, VWF:Ag is reduced, as is the functional activity of VWF. The VWF:RCo assay is still considered the gold standard for measuring the activity of VWF, especially the VWF-dependent platelet adhesion activity. If the VWF:RCo/VWF:Ag ratio is >0.6 the diagnosis of type 1 VWD is made. In case of a ratio ≤0.6 this is indicative of type 2 VWD. Additional testes like VWF multimer analysis by gel-electrophoresis and ristocetin-induced platelet aggregation (RIPA) are necessary to further subtype type 2 patients in type 2A, 2B and 2M. The assay to study binding of VWF to collagen (VWF:CB) is can be used identify type 2M with specific VWF defects in binding to collagen. FVIII:C is also reduced in VWD, because VWF binds FVIII in circulation, thereby protecting it from degradation. In type 2N (Normandy) FVIII:C is reduced more strongly VWF:Ag. Type 2N can be confirmed by measuring FVIII binding to VWF (VWF:FVIIIB). In recent years VWF propeptide (VWFpp) has been used to improve diagnosis of subtypes of VWD. In type 3 patients very low levels of VWF:Ag and VWFpp are found, whereas type 1 patients with very low VWF:Ag levels, VWFpp is mildly reduced or even normal. Although the VWFpp assay is not (yet) part of the official classification scheme of VWD, it can be used to classify VWF variants with increased clearance, based on a relative increase of VWFpp over VWF:Ag.

New tests to measure the platelet-binding function of VWF are more frequently used because of the low sensitivity of the VWF:RCo test. The ristocetin VWF:GPIbR assay measures the binding of VWF to a recombinant wild-type glycoprotein Ibα fragment and the VWF:GPIbM assay uses the spontaneous binding of VWF to a gain-of-function recombinant mutant glycoprotein Ibα fragment. These assays reflect the platelet binding activity of VWF and correlate well with the VWF:RCo assay results. In some patients discrepancies between the various activity assays may be present, which can be attributed to specific function defects. Genotyping of *VWF* is not performed routinely in the diagnosis of VWD, but may be useful to diagnose type 2N and 2B. In families with type 3, genetic analysis may be useful for counseling. During the meeting recent data on the new assays will be presented, as well as the most recent recommendations of the ISTH-SSC.