

The laboratory diagnosis of von Willebrand Disease: current insights

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Von Willebrand Disease (VWD) is the most common inherited bleeding disorder worldwide, affecting up to 0.5-1% of the population. VWD is caused by defects in or reduced levels of Von Willebrand Factor (VWF). VWF plays a major role in primary hemostasis by facilitating adhesion of platelets to the endothelium, thereby initiating aggregation of platelets to form a platelet plug. In addition VWF is the carrier protein of factor VIII. Whereas type 1 VWD is characterized by a partial quantitative deficiency of VWF, qualitatively abnormal variants of VWF are classified as type 2 VWD. Type 3 VWD is characterized by a total deficiency of VWF.

The diagnosis of VWD is based on the presence of mucocutaneous bleeding symptoms, reduced circulating VWF levels, and an autosomal dominant or recessive inheritance. Patients with VWD frequently have bleeding episodes, varying from gum bleeds and epistaxis to intestinal bleeding, and in severe VWD also joint bleeding may occur.

In case of a bleeding diathesis a screening test for disorders in primary hemostasis is performed, for example PFA-100®. These tests have replaced the bleeding time in most laboratories. Laboratory diagnosis of VWD is based on the measurement of Von Willebrand factor antigen levels (VWF:Ag), VWF ristocetin-cofactor activity (VWF:RCo) and FVIII:C levels. Sometimes also VWF collagen binding activity (VWF:CB) is determined. In case of a suspicious medical history for a bleeding disorder, testing should be performed at least three times. If the patient's results are suggestive of the diagnosis VWD, multimer analysis and a ristocetin induced platelet agglutination (RIPA) test is performed to classify the type of VWD, according to the current ISTH guidelines. Type 1 VWD is diagnosed in case of a VWF RCo:Ag > 0.7 and normal multimers. Type 2 is diagnosed if the ratio is <0.7, frequently in combination with an abnormal multimer pattern. Several subtypes of type 2 (2A, 2B, 2M, 2N) can be distinguished, based on the multimer pattern. Type 3 is diagnosed if no VWF is present in plasma. Genetic testing for VWD is not performed routinely in the Netherlands. If type 2 VWD is suspected or diagnosed, genotyping is sometimes performed to distinguish between types 2A and 2B, and between type 2B and platelet-type VWD. This is especially performed in those individuals who do not have all typical characteristics of type 2B. Another reason for genetic testing is to differentiate between hemophilia A and VWD type 2N.

Until recently, most VWF tests were ELISAs that were elaborate to perform and results were not available at short notice. In the last few years several new assays have been developed for measuring the antigen and activity levels of VWF. Some of these assays can be performed on coagulation analyzers and results can be available rapidly. The performance of these new assays will be discussed in the presentation.