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Novel insights in the diagnosis and classification of autosomal recessive and dominant von Willebrand diseases anno 2018

The European Clinica Laboratory and Molecular (ECLM) criteria define 10 distinct von Willebrand diseases (VWD) due to mutations in the D1, D2, D', D3, A1, A2, A3, D4, C1-6 and CK domains of the von Willebrand factor (VWF) gene: recessive VWD type 3, severe type 1, 2C and 2N; dominant VWD type 1 clearance (C), secretion (SD) or clearance/secretion defect (CSD); dominant VWD 2A, 2B, 2E, 2M and 2D; and mild type 1 (Low VWF) frequentl carriers of recessive VWD. Recessive VWD type 3 is caused by homozygous or heterozygous double null mutations as the cause of recessive pseudo-hemophilia first described by Erik von Willebrand. Recessive VWDs type 1 are mainly caused by homozygous or double heterozygous missense secretion defective mutations in the D1, D2, D4 or C1-6 domains of the VWF gene. Recessive VWD due to mutations in the D1 domain is featured by persistence of pro-VWF and characterized by severe secretion and FVIII binding defect and therefore mimicking VWD type 3. Recessive VWD 2C due to mutations in the D2 domain are featured by secretion and multimerization defect and no clearance defect. Recessive VWD 2N is a mild hemophilia due to mutations in the D'-FVIII binding domain. The VWF function and multimers are normal in noncysteine 2N mutations and defective in cystein 2N mutations in the D'domain, whereas the 1060 2N mutation in the D3 show a hybrid 2N/2E VWD phenotype. Dominant VWD 1E or 2E are caused by heterozygous missense mutations in the D3 domain and are featured by variable degrees of secretion (SD) multimerization and clearance (C) defects. VWD 1C as the most pronounced clearance defect is caused by the Vincenza mutation R1205H in the D3 domain. Dominant VWD 2B is caused by a gain of function mutation in the A1 domain showing spontaneous interaction between VWD 2B mutant and platelet glycoprotein Ib (GPIb) with the consequence of increased ristocetine-induced platelet aggregation (RIPA) followed by increased proteolysis at the VWF cleavage site leading to the loss of large VWF multimers mimicking VWD type 2A. Dominant VWD 2M is due to loss of RIPA function mutations in the A1 domain and characterized by decreased (RIPA), decreased VWF:RCo as compared to VWF:CB (I-III), with normal or smeary VWF multimers or some loss of large mutimers, a poor response of VWF:RCo and normal response of VWF:CB to DDAVP. Dominant VWD type 2A are hypersensitive to ADAMTS13 (VWF cleavage protein) caused by mutations in the A2 domain of the VWF gene, which results in proteolysis of large VWF multimers by ADAMTS13 into VWF degradation products resulting in the loss of large VWF multimers, triplet structure of VWF bands and decreased ratios of both VWF:RCo/Ag and VWF:CB/Ag. A new category of secretion and/or clearance defects are due to mutations in the D4 and C1-6 domains. The D4 and C1-6 mutations in the VWF gene mainly consist of two groups of VWD type 1 secretion defects (SD) those with normal VWF multimers and those with a smeary VWF multimeric pattern. Homozygosity or double heterozygosity null or missense mutation in the C1-6 domain produce recessive severe type 1 VWD with smeary VWF multimers (eg mutation 2362). VWD mutations in the CK dimerization domain of the VWF gene produce dominant or recessive VWD type 2D (or even recessive type 1) featured by the loss of large VWF multimers and intervening VWF subbands.

Speaker Biography

Jan Michiels Professor of Nature Medicine & Health Blood Coagulation & Vascular Medicine Center in Netherlands. He also serves as an Editorial board member for many scientific journals

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