Type 1 von Willebrand disease due to reduced von Willebrand factor synthesis and/or survival: observations from a case series

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It may be difficult to diagnose type 1 von Willebrand disease (VWD) because of its heterogeneous and sometimes elusive nature. To evaluate the contribution of a shorter von Willebrand factor (VWF) survival in modulating VWD phenotype, the VWF half-life was assessed in 45 type 1 VWD patients using a 24-h 1-desamino-8-d-arginine vasopressin (DDAVP) test. A shorter VWF survival was observed in patients with C1130F mutations ($T_{1/2}$ elimination ($T_{1/2}$el) = 4.6 ± 1.0 h vs normal = 15.8 ± 2.3 h, $P < 0.0001$), in those with other missense mutations investigated ($T_{1/2}$el = 9.5 ± 0.9 h, $P < 0.02$), and in patients not carrying VWF mutations ($T_{1/2}$el = 7.0 ± 0.7 h, $P < 0.001$); the decrease mainly depended on a greater VWF clearance. VWF survival and clearance were normal in patients who carried nonsense mutations. The VWF-propeptide-to-VWF-antigen (VWF:Ag) ratio (VWFpp ratio) was higher in patients with a shorter VWF survival, and the values were inversely correlated with the VWF half-life ($P < 0.01$). The response of VWF to DDAVP administration, which is useful to explore the synthesis and storage of VWF, was normal in patients with no mutations, whereas it decreased in patients with missense and nonsense mutations. Three scenarios, thus, are recognizable in type 1 VWD; one is associated mainly with a shorter survival of VWF, another is associated with its reduced synthesis and release, and a third is characterized by a combination of the two. The shorter VWF half-life found in patients with no VWF mutations suggests that mechanisms other than VWF might be involved in the pathogenesis of type 1 VWD. (Translational Research 2010;155:200–208)

Abbreviations: CL = clearance; DDAVP = 1-desamino-8-d-arginine vasopressin; ELISA = enzyme-linked immunosorbant assay; FVIII = Factor VIII; HRP = horseradish peroxidase; PBS = phosphate-buffered saline; $T_{1/2}$el = $T_{1/2}$ elimination; Vre = velocity of release; VWD = von Willebrand disease; VWF = von Willebrand factor; VWF:Ag = VWF antigen; VWF:CB = VWF collagen binding; VWF:CB ratio = VWF:CB/VWF:Ag ratio; VWFpp = VWF propeptide; VWFpp ratio = VWF pp/VWF:Ag ratio; VWF:RCo = VWF ristocetin cofactor; VWF:RCo ratio = VWF:RCo/VWF:Ag ratio

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AT A GLANCE COMMENTARY

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Background

von Willebrand disease (VWD) is a heterogeneous inherited bleeding disorder caused by von Willebrand factor (VWF) anomalies. Shorter VWF survival has been shown recently to be a cause of type Vicenza VWD being the archetype of such forms.

Translational Significance

We investigated how a shorter VWF half-life contributed to type 1 VWD—the most common and heterogeneous form of VWD. Demonstrating that an increased VWF clearance is part of the type 1 VWD phenotype not only helps to predict the bleeding risk of these patients but also helps orient their therapy, which cannot involve the use of the vasopressin analog 1-desamino-8-d-arginine vasopressin.

Von Willebrand disease (VWD) is the most common inherited bleeding disorder[1] and is caused by a shortage or anomalies of the von Willebrand factor (VWF)—a large multimeric glycoprotein that mediates the adhesion and aggregation of platelets to the subendothelium and stabilizes circulating factor VIII (FVIII).[2,3] VWF occurs in blood plasma, platelet alpha-granules, the Weibel–Palade bodies of endothelial cells, and the subendothelial matrix, and it is synthesized by megakaryocytes and endothelial cells.[4] VWF synthesis and release by endothelial cells guarantee circulating VWF concentrations, whereas platelet VWF serves local needs.[5] One main feature of VWF is its complex multimeric structure, which is characterized by oligomers that range from 500,000 to more than 20 million daltons, and the largest VWF multimers are the most active hemostatically.[6] The multimeric structure of VWF is the outcome of a sequential process of dimerization, which involves the C-terminal portion of VWF and the multimerization of dimers through the N-terminal portion. Although VWF is not an enzyme, it nonetheless can promote self-polymerization through its CXXC sequence in the D2 domain of the VWF propeptide, which resembles the functional site C of the thiol disulphide oxidoreductase.[7]

The propeptide of VWF (VWFpp) is a 741 amino acid fragment that remains linked covalently to VWF after its cleavage from mature VWF in the post-Golgi compartment.[8-10] VWF and VWFpp are released together in 1:1 stoichiometric amounts. After dissociating from mature VWF, the VWFpp circulates as a dimer with a 2-h half-life, as opposed to the 10–20 h of mature VWF.[11] It has been reported recently that the steady-state ratio of VWFpp to VWF antigen (VWF:Ag) (VWFpp ratio) is useful to identify a shorter VWF survival in cases of VWD.[12-14]

The current classification of VWD,[1] which is based on an altered VWF synthesis and/or function, includes the following 3 types of VWD: type 1 VWD depends on a reduction in VWF concentration with a homogeneous decline in VWF function and no important structural VWF anomalies,[15] and it accounts for at least 60% of all cases of VWD[16]; type 3 coincides with the virtual absence of VWF; and type 2 group includes VWF anomalies with a prevalent functional defect, with 4 main subtypes (types 2A, 2B, 2 M, and 2 N) associated with altered VWF-Glycoprotein Ib (VWF-GPIb) interactions or defects in FVIII binding to VWF.[17] More recently, a decline in the VWF half-life has been found responsible for causing or exacerbating VWD.[18-20] The now accepted classification[1] differs from its predecessor[21] in that VWD is no longer a definition restricted to patients with VWF gene mutations.

Here, we analyzed the contribution of an impaired VWF survival in modulating type 1 VWD.

MATERIALS AND METHODS

Healthy volunteers and VWD patients were studied in accordance with the Helsinki Declaration after obtaining their informed consent in writing and study approval from the Institutional Review Board at the University of Padua Medical School.

Blood was drawn from the antecubital vein and anticoagulated using sodium citrate 3.8% (1:10, vol/vol). VWF:Ag was measured with a homemade, enzyme-linked immunosorbant assay (ELISA) method, using a horseradish peroxidase (HRP)-conjugated anti-VWF antibody (Dako, Glostrup, Denmark). FVIII coagulant was measured using a 1-stage method, with cephaloplastin as the activated cephalin. VWF collagen binding (VWF:CB) activity was assessed by ELISA using type I and type III collagen diluted in acetic acid solutions (95% and 5%, respectively).[22] Briefly, after overnight coating with collagen, microtiter plates were incubated with plasma VWF for 1 h at room temperature; bound VWF was evaluated with an HRP-conjugated anti-VWF antibody. The coefficient of variation (CV) of the assay was calculated to be 8.5%. The VWF ristocetin cofactor (VWF:RCo) was measured using normal washed, formalin-fixed, platelets and 1.0 mg/mL ristocetin in a Chronolog aggregometer. VWFpp concentrations were determined using an ELISA test supplied by GTI Diagnostics (Waukesha, Wis).[14] Briefly, prediluted calibrators and diluted plasma samples were added to