von Willebrand Factor: A Tool to Predict Severity and Prognosis in Liver Disease

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Abstract
Von Willebrand factor (vWF) is an adhesive and multimeric glycoprotein that has a central role in primary hemostasis. vWF levels correlate with thrombosis risk and inversely with bleeding risk within the apparently healthy population. Recently, numerous publications in Indian and western literature have focussed to its role in liver diseases like acute liver failure, chronic liver disease, non cirrhotic portal hypertension and tropical infections eg. dengue. The present review encapsulates the recent advances in this aspect.

Introduction
Von Willebrand factor (vWF) is an adhesive and multimeric glycoprotein that found its historical origin in 1924, when the Finnish physician Erik von Willebrand first reported a family with a serious hereditary bleeding amongst consanguineous families.

Molecular Structure
vWF gene was cloned in 1985 using endothelial cell cDNA libraries. The gene is located on the short arm of chromosome 12 at the locus 12p13.3 and spans 178 kilobases. The human vWF gene contains 52 exons and the exon 28 is the largest, its length is 1.4 kb.

Analysis of the amino acid sequence shows four distinct domains that are each repeated from two to four times. There are three A-domains, three B-domains, two C-domains and four D-domains. The D'-D3 domains exhibit a binding site for factor VIII (FVIII), heparin and P selectin. The A1 domain is the only known binding site for the platelet receptor glycoprotein (GP) Ibα, and contains additional binding site for heparin, sulphated glycolipids and the snake venom botocetin. The A2 domain contains the cleavage site for the metalloprotease ADAMTS-13. The A3 domain is the binding site for fibrillar collagen type I and III. The C1 domain which comprises the RGD sequence is the binding site for the integrin αIIbβ3.

Functions
vWF has a central role in primary haemostasis. It mediates platelet adhesion to the damaged vascular sub endothelium and thereby promotes platelet aggregation.

vWF is an adhesive plasma glycoprotein that enables haemostatic functions through its binding capability to FVIII, platelet surface glycoproteins and to constituents of connective tissue. It serves as a FVIII stabilizer in the circulation and the vWF-FVIII complex protects FVIII from degradation by activated protein C. Further, it mobilises FVIII to sites of platelet plug and clot formation. vWF by blocking the interaction of FVIII with lipoprotein-related receptors enhances the half life of FVIII in the circulation.

Plasma vWF exists as multimers of various sizes. Ultra-large vWF multimers can be detected transiently in normal plasma. The latter are hyperactive in binding the platelet receptor GPIb-IX-V complex, resulting in spontaneous platelet aggregation and therefore need rapid extraction from plasma of in a healthy individual.

The regulation of size of plasma vWF is by specific proteolytic process referred to as metalloprotease ADAMTS-13. Severe deficiency of ADAMTS-13 activity may result in thrombotic thrombocytopenic purpura (TTP) and mutation in the A2 domain enhances the susceptibility of vWF to cleavage that manifests as von Willebrand Disease (VWD) type 2A.

vWF level correlates with greater risk for thrombosis and inversely with bleeding rates in an apparently healthy population. These risks vary continuously and reciprocally across the normal range of VWF levels, with no clear cut demarcation or cut off between a normal and a pathological risk for these adverse events.

vWF in liver disease
Acute liver failure
Hugenholtz et al assessed levels and functionality of von Willebrand factor (VWF) and ADAMTS13 in the plasma of patients with acute liver injury and acute liver failure(ALI/ALF). The levels of vWF antigen were grossly elevated in these patients. The proportion of high molecular weight vWF multimers were reduced, despite extreme reduction of ADAMTS13 levels. The authors concluded that extreme elevated levels of VWF in plasma of patients with ALI/ALF supported platelet adhesion, despite a relative loss of function of the molecule.

Cirrhosis and portal hypertension
vWF-Ag in recent times is considered as a simple and noninvasive predictor of clinically significant portal hypertension (CSPH). It correlates well with liver function and hepatic venous pressure gradient and independently predicts clinical outcome. VITRO score (the VWF-Ag/platelet ratio) is a good tool to diagnose CSPH.

A vWF-Ag cut-off value at 315% stratifies patients with compensated and decompensated liver cirrhosis.
Compensated patients had 25% mortality after 53 months if the vWF-Ag was <315% compared to 15 months in patients with vWF-Ag >315% (P < 0.001). Decompensated patients had a mortality of 25% after 37 and 7 months if their vWF-Ag was <315% and >315%, respectively (P = 0.002). In compensated patients with a vWF-Ag >315% median time to decompensation or death was 32 months compared with 59 months in patients with vWF-Ag <315%. vWF-Ag was also similar to Model for End-Stage Liver Disease (MELD) in mortality prediction. Thus, it can be considered to be a valuable biomarker for predicting mortality in cirrhotic patients.  

Indian contribution

Eapen et al reported association of vWF and ADAMTS13 in patients with noncirrhotic portal hypertension (NCIPH). They reported deficiency of ADAMTS13 and presence of ultra large vWF multimers in these patients as well as in those with portopulmonary hypertension. The same authors have reported that ADAMTS13 deficiency in NCIPH in patients with relatively preserved liver function was probably responsible for morphological changes in NCIPH.

In a study on patients with ACLF, the same centre reported markedly elevated vWF which correlated with organ failure and predicted survival in these patients. The vWF activity and not vWF antigen correlated with liver disease severity (MELD score, ACLF grade) and organ failure (Sequential Organ Failure Assessment [SOFA] score). The authors postulated in this publication that vWF-reducing treatments such as plasma exchange may benefit ACLF patients.

More recently, Eapen et al have proposed ADAMTS13 deficiency as a possible marker for predicting worsening of patients with severe dengue infection.

Conclusion

vWF level correlates with thrombosis risk and inversely with bleeding risk within the apparently healthy population. The impact of abnormalities of VWF on liver disease and its outcome has now been well documented. Research in required to device procedures and treatments that would enable physicians to use this knowledge for the benefit of their patients.

References