

ABO(H) association with vWF level: a brief literature review

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2008 is marked by completion of a long line of inquiry into why type O individuals tend to have lower vWF levels than non-O individuals. This association has challenged us in terms of understanding vWF physiology, and also coming to grips with defining a disease.

The story began in earnest in 1993, when Matsui and co-workers observed that vWF protein of blood group A individuals expressed the A oligosaccharide antigen. They demonstrated that this ABO group antigen is associated with the vWF protein via a type 2 chain, now recognised as an N-linked glycan. Bowen picked up the thread in 2002 with the observation that vWF from blood group O individuals is more susceptible to the hydrolytic effect of the cleaving protease ADAMTS13 when compared to non-O plasma. This effect was measured by cleavage of HMWMs of vWF and by consequent loss of collagen binding ability over time. Bowen hypothesised that the two N-linked glycans flanking the vWF A2 domain-based cleavage site for ADAMTS13 effectively regulate interaction between the metalloprotease and its ligand. In other words, presence of the A or B blood group oligosaccharides within the A2 domain of vWF limits ability of vWF to be cleaved by ADAMTS13. Conversely, absence of these large N-linked glycan structures in group O individuals renders vWF more susceptible to degradation by ADAMTS13. It would seem logical that plasma lacking the H antigen (the essential precursor structure that is expressed in all ABO(H) types and subsequently converted into the A or B antigens depending on blood group) – the Bombay phenotype – should have even lower vWF levels than group O individuals. This was indeed found by O'Donnell et al, who very nicely demonstrated that vWF in Bombay phenotype plasma showed enhanced susceptibility to the effect of ADAMTS13, compared to group O plasma. The same group (McKinnon et al) described very eloquently in 2008 the detail of the two N-linked ABO group glycans and their regulatory effect on vWF interaction with its cleaving protease.

The above in vitro elucidation of the regulation of vWF levels by blood group antigens invited an in vivo demonstration. This was provided in a delightfully simple way by Gallinaro et al in 2008. Proving that ingenuity is even more important than technical difficulty to get published in BLOOD, they took individuals from different ABO groups and administered DDAVP, measuring the half life of vWF. As predicted by the in vitro work, they found shorter vWF half life in group O individuals.

These publications have challenged our concept of von Willebrand disease (vWD). International registries have shown that the phenotype of vWD does not always track with a mutation of the vWF gene. Now, we have conclusive proof that vWF levels also reflect rate of vWF degradation, influenced by ABO group. How then do we most accurately make a diagnosis of vWD? Tosetto et al apply a rigorously logical approach based upon Bayes theorem. Starting

with a conservative estimate of 0.1% disease prevalence, the odds ratio of a person having vWD is then modified by calculated likelihood ratios based on an objective bleeding score, on vWF levels and on number of first degree family members sharing a deficiency of vWF. This arguably complex approach fits well with the recommendation by Lipton on how to handle those who do not fit easily into a label of vWD: in the same way that sunscreen is advised for fair-skinned people to prevent risks of sunburn, DDAVP where appropriate will reduce peri-operative bleeding risk in people with mildly reduced vWF levels.

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Gallinaro L et al. A shorter von Willebrand factor survival in O blood group subjects explains how ABO determinants influence plasma von Willebrand factor. *Blood* 2008;111:3540-3545.

Lipton R. Why make a diagnosis? *BLOOD* 2007;109:4106.

Matsui T et al. Human plasma α -2 macroglobulin and von Willebrand factor possess covalently linked ABO(H) blood group antigens in subjects with corresponding ABO phenotype. *BLOOD* 1993;82(2):663-668.

McKinnon TAJ et al. N-linked glycosylation of VWF modulates its interaction with ADAMTS13. *Blood* 2008;111(6):3042-3049.

O'Donnell JS et al. Bombay phenotype is associated with reduced plasma-VWF level;s and an increased susceptibility to ADAMTS13 proteolysis. *BLOOD* 2005;106(6):1988-1991.

Tosetto A et al. Evidence-based diagnosis of type 1 von Willebrand disease: a Bayes theorem approach. *Blood* 2008;111:3998 – 4003.