Combined hemophilia A and type 2N von Willebrand's disease: defect of both factor VIII level and factor VIII binding capacity of von Willebrand factor

We describe a family in which hemophilia A and von Willebrand's disease (VWD) were simultaneously present.

von Willebrand's disease (VWD) and hemophilia A are the most common inherited bleeding disorders,[1] having factor VIII (FVIII) deficiency in common, albeit of different origin. In hemophilia A, the FVIII defect is associated with abnormalities in the FVIII gene, with an X-linked pattern of transmission, whereas in VWD the deficiency is related to an abnormality in von Willebrand factor (VWF), encoded by a gene located in chromosome 12. VWF carries FVIII[2] and its reduction/absence reduces FVIII plasma concentration. Type 2N is a VWD variant characterized by a defect in the FVIII binding function of VWF,[3] (with reduced FVIII but normal VWF levels. It may be misdiagnosed as hemophilia A.[4]

We describe a family (Figure 1) in which hemophilia A and VWD were simultaneously present: a hemophilic man (I-2) married a woman heterozygous for type 2N VWD (I-3) and their daughter (II-1) was both a carrier of hemophilia A and heterozygous for type 2N VWD. The main hemostatic findings in these subjects are reported in the Table. The proband (II-1) showed a prolonged aPTT, decreased FVIII activity (43 U/dL vs normal range 60-160 U/dL) and low FVIII/VWF:Ag ratio (0.27 vs normal > 0.8), with a normal VWF:Ag level. VWF:FVIIIB, a test which evaluates FVIII binding capacity of VWF,[5] was normal when expressed as an absolute value (89.7 U/dL vs normal range 70-140 U/dL) but decreased when expressed as the ratio of VWF:FVIIIB to VWF:Ag (0.55 vs normal > 0.75). This finding suggests that FVIII binding activity was less than expected on the basis of the VWF level. The proband's mother and half-sister (II-2) had normal aPTT, FVIII, FVIII/VWF:Ag ratio and VWF:FVIIIB, but a decreased VWF:FVIIIB ratio (0.56 and 0.61, respectively). The proband's hemophilic uncle had decreased FVIII levels but normal FVIII binding capacity of VWF (Table 1).

DNA sequencing of exon 20 gene revealed that the proband, her mother, and sister had a single point mutation G2811A (nucleotide numbering including untranslated exon 1) on one allele. This substitution introduces the most frequent type 2N mutation, Arg91Gln, in the mature VWF protein.[6] Therefore, the proband appeared to be heterozygous for type 2N VWD and also a carrier of hemophilia A, while her mother and sister were heterozygous for type 2N VWD only. No Arg91Gln mutation was found in the uncle, in agreement with his normal FVIII binding capacity. The father could not be studied because he had died before the time of this study.

Due to the fact that VWD and hemophilia A are the most common inherited bleeding disorders, and that heretozygotes for type 2N are relatively frequent in the normal population, the possibility of a combined defect must be considered in the diagnostic procedures, as well as in the differential diagnosis between hemophilia A and type 2N VWD. Even though a combination of the two defects, at heterozygous level, does not seem to increase the tendency to bleed, as observed in isolated type 2N VWD or hemophila A carriers, its identification has great implications in genetic counselling.

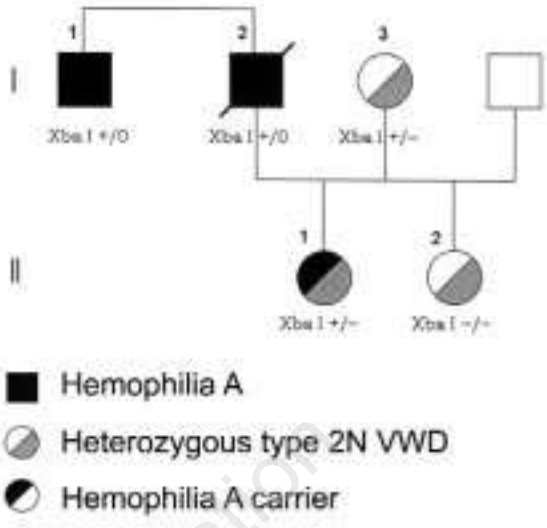

Figure 1. Hemophilia A is associated with the restriction site XbaI in intron 22 of FVIII gene, investigated by means of intragenic restriction fragment polymorphism (RFLP) analysis.

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Table 1.

Patients	*aPTT sec.*	*FVIII U/dL*	*VWF:Ag U/dL*	*VWF:RCo U/dL*	*FVIII/VWF:Ag ratio*	*VWF:FVIIIBA U/dL*	*VWF:FVIIIB/VWF:Ag ratio*
I-1	74	1.8	142	127	0.02	129	0.9
I-2	76.5	2.0	105	NP	0.03	NP	NP
I-3	36	93	106	90.2	0.88	62.5	0.59
II-1	44.5	43	159.8	134	0.27	89.7	0.56
II-2	32.4	114	138.7	123.5	0.82	84.6	0.61
Normal range	33-42	60-160	60-160	60-130	≥0.8	70-140	≥0.75

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