

Are thrombotic complications in patients with von Willebrand's disease expression of a multifactorial disease?

Here we report an episode of venous thromboembolism (VTE) complicating surgery in a patient with von Willebrand disease (VWD).

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The patient, a 68-year old female with type 1 VWD (VWF antigen [VWF:Ag] 16 IU/dL, ristocetin cofactor [VWF:RCo] 20 IU/dL, coagulant factor VIII [FVIII:C] 15 IU/dL) responsive to desmopressin (DDAVP) and heterozygous for factor V Leiden and prothrombin G20210A mutations, experienced a pulmonary embolism during a hip replacement operation. She had been given 3000 FVIII IU of FVIII/VWF concentrate (Emoclot, Kedrion, Italy) one hour prior to the operation. DDAVP was not used as prophylaxis against bleeding because the patient had hypertension and coronary artery disease. The thrombotic event was successfully treated with a continuous infusion of unfractionated heparin (18 U/Kg/hour for 7 days) followed by 6 months of oral anticoagulation to maintain the international normalized ratio (INR) between 2 and 3. Postoperatively, the patient continued to receive the same FVIII/VWF concentrate at a dose of 2000 FVIII IU/daily from day +1 to day +12.

It could seem paradoxical to speak of thrombotic events in patients with inherited bleeding disorders. In fact, as expected, *naturally* anticoagulated patients very infrequently experience thrombotic events and there are only a few published reports describing spontaneous myocardial infarction, cerebrovascular accidents or venous thrombosis in patients with inherited bleeding disorders.¹ However, in some cases the coexistence of acquired or inherited prothrombotic risk factors may overcome the bleeding tendency and lead to the development of thrombotic complications in VWD patients.¹ The infusion, as prophylaxis or treatment of hemorrhage, of intermediate purity clotting factor concentrates containing factor VIII (FVIII) and von Willebrand factor (VWF) is one of the most important risk factors for thrombosis in VWD patients since serial exogenous FVIII and VWF administrations added to normal endogenous FVIII synthesis are responsible for high FVIII levels (> 150 UI/dL), which are a well known risk factor for VTE.² Mannucci³ and Makris⁴ reported 11 cases of venous thromboembolism in VWD patients following FVIII/VWF concentrate infusion. However, in all cases but one additional prothrombotic risk factors (i.e., estrogen intake, surgery, obesity) were present. Moreover, both authors (Makris and Mannucci) outlined the importance of using the FVIII/VWF concentrate with the highest ratio between VWF:RCo and FVIII:C in such patients, in order to correct the VWF defect without increasing FVIII:C plasma levels excessively. We have previously reported two thrombotic episodes (one venous and one arterial) occurring in VWD patients who were also carriers of pro-

thrombotic gene mutations.^{5,6} In the first case, a 26-year old male patient with type I VWD, double heterozygous for the C677T and A1298C mutations in the MTHFR gene and heterozygous for the 455G/A mutation in the α -fibrinogen gene, experienced a popliteal vein thrombosis after orthopedic surgery for which he was treated with desmopressin. In the second case, we found coronary artery occlusion in a 53-year old man with type I VWD and smoking, hypertension, hypercholesterolemia and heterozygosity for the prothrombin G20210A and MTHFR C677T mutations as prothrombotic risk factors.

In the present case, while the high post-infusion FVIII levels detected (180 UI/dL) were due to the relatively high FVIII/VWF content of the concentrate used (VWF:RCo/FVIII:C ratio of 2.54),⁷ the presence of several other thrombotic risk factors (i.e., old age, hypertension, obesity, orthopedic surgery) further confirms that thrombotic complications in VWD patients have in most cases, if not all, a multifactorial origin. Thus, in such patients careful weighing of prothrombotic risk factors should guide the choice of antithrombotic prophylaxis in high-risk thrombotic situations (e.g., major orthopedic surgery).

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