case report

Von Willebrand disease type 2B with a novel mutation in the VWF gene

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We report a 38-year-old woman who presented with a subdural hematoma after minor facial trauma in a stressful situation. The laboratory data showed a subnormal platelet count (166×10^9/L), VWF:RCo activity was 45% and VWF:Ag was 53% with a VWF:RCo/VWF Ag ratio of 0.79. Hemostasis results and gene analysis revealed von Willebrand disease (VWD) type 2B with normal multimers and a novel mutation c.4136 G>T (R1379L), which appears to be a novel mutation of VWD type 2B that is mainly diagnosed with hypersensitivity to ristocetin and an hyperfixation of platelet Willebrand to a recombinant Gp1b.

SIMILAR CASES PUBLISHED: None.

Von Willebrand disease (VWD), type 2B is an uncommon condition with an autosomal dominant pattern of inheritance. The disease is characterized by a dysfunctional von Willebrand factor (VWF) protein. This leads to an enhanced affinity to platelets and increased ADAMTS13-mediated proteolysis of VWF resulting in the clearance of the high molecular weight multimers (HMWM) of VWF with consequences of thrombocytopenia and a bleeding disorder.[1-3] This defect is caused by mutations in the A1 region, encoded by exon 28 of the VWF gene.[4-7] Type 2B disease is diagnosed based on low levels of von Willebrand factor ristocetin cofactor (VWF:RCo) activity and antigen (VWF:Ag) with a RCo:Ag ratio <0.7, an increased responsiveness to ristocetin, thrombocytopenia and loss of HMWM. However, some type 2B patients have a normal VWF multimer pattern.[8,9] Recently Casonato A et al distinguished type 2B VWD patients according to their multimer structure and classified by type 2B-I, who lacked large multimers and type 2B-II, who had a normal VWF multimer pattern.[10] We report a type 2B VWD related to a novel mutation found in exon 28 of the VWF gene with the locus at position 1379.

CASE

We present a case of a 38-year-old woman, with no history of heavy menstrual period and no epistaxis. The patient gave a history of multiple dental extractions and three vaginal deliveries with no bleeding complications. But she presented with a subdural hematoma after a minor trauma. She did not take any anticoagulants or antiplatelet therapy and did not suffer from hypertension. She also had a previous breast reduction surgery and hand surgery with postoperative bleeding. The bleeding score was 4 by the Vicenza Bleeding Questionnaire using the European Molecular and Clinical Markers for the Diagnosis and Management of type 1 VWD (MCMDM-1 VWD). [11]

Table 1. Hemostatic parameters of the patient and her family.

Family	FVIII	Platelet 10^9/L	vWF:Ag	vWF:RCo	vWF:Rco ratio	vWF:CB	Plasma vWF Gp1b	Platelet vWF GP1b	RIPA (+) lowest Rist (mg/mL)	PFA100 (Second) Epi	PFA100 (Second) ADP	vWF mutation
Patient (Visit 1)	82%	166	53%	45%	0.79	86%	N	↑	0.5	123	92	R1379L
Patient (Visit 2)	55%	196	57%	49%	0.92	47%	N	↑	0.6	148	123	R1379L
Son 1	81%	306	70%	95%	0.89	92%	N	↑	0.5	170	105	R1379L
Son 2 (minimal epistaxis)	68%	218	68%	77%	0.91	98%	N	↑	0.5	196	157	R1379L
Daughter	105%	214	111%	130%	0.97	NA	N	N	0.8	117	NA	No
Normal range	70-150	185-445	50-150	50-150	>0.7	50-150	N	N	RIPA(+) below 0.8	82-150	62-100	

N1=Normal; NA=Not assessed.

The initial laboratory evaluation revealed a normal coagulation test (PT, aPTT, fibrinogen), a subnormal platelet count (166×10⁹/L), (VWF:RCo activity was 45% and VWF:Ag was 53% with a VWF:RCo/VWF:Ag ratio of 0.79. The multimeric forms of the VWF were separated via gel electrophoresis with 0.1% sodium dodecyl sulfate and 1.5 % agarose. The multimers detected by colorimetry with direct immunological staining had a normal multimeric structure. Her blood group was A.

The type 2B VWD diagnosis relied on enhanced ristocetin-induced platelet aggregation (RIPA) with ristocetin concentration 0.5 mg/mL and 0.6 mg/mL (<.07 mg/dL is diagnostic for type 2B VWD) and a hyperfixation of platelet VWF to GP1b with no hyperfixation of plasma VWF. Surprisingly, there was no decrease in the platelet count 2 hours after vasopressin administration. Nucleotide sequence analysis of exon 28 of the VWF gene showed a heterozygous mutation c.4136 G>T (p. R1379 L). Her mother and brother suffered from epistaxis; we do not know their mutation status. Two sons carried the same mutation, but only one presented with minimal epistaxis. Neither had a surgical procedure. Their biological characteristics are shown in **Table 1**.

DISCUSSION

VWD is the most common inherited bleeding disorder.[12] It is classified on the basis of the VWF:RCo/Ag ratio, the multimeric profile, platelet count and ristocetin-induced platelet agglutination. Type 2B accounts for approximately 5% of cases and is related to numerous mutations in exon 28 of the VWF gene.[13] We report a novel heterozygous missense mutation in the VWF gene (p.R1379L), a single substitution (G>T) that gives a leucine instead of the normal arginine, located at nucleotide 4136. The mutation is responsible for this type 2B VWD, which is mainly diagnosed with hypersensitivity to ristocetin and a hyperfixation of platelet VWF to a recombinant Gp1b. No such mutation has previously been reported. However, a mutation at the same site has been reported (R1379C), in which a cysteine replaces the normal arginine. This mutation was reported recently by Casonato et al as VWD type 2B-II in six patients with a normal multimeric structure associated with thrombocytopenia. Our patient presented with subdural hematoma after minor facial trauma. We did not know her platelet count at the time of hematoma.

In type 2B VWD, VWF interacts with platelets depending on their platelet count while the disappearance of large VWF multimers is associated with transient or persistent thrombocytopenia.[14] The degree of thrombocytopenia can vary and may be aggravated at

times of increased VWF production or secretion, such as during physical effort, inflammation, or pregnancy and another independent risk factor for bleeding in patients with VWD 2B. Thrombocytopenia may be triggered by stressful situations.[15] In one study, patients with thrombocytopenia had a five times higher risk of bleeding than patients with a normal platelet count.[16]

VWF may have a greater affinity for platelets despite the presence of a normal multimer pattern in 2B VWD, as seen in variants such as type New York, Sussman II, type Malmo, and others.[17,18] These conditions differ from type 2B VWD not only in the associated VWF multimer pattern, but also in that patients never suffer from thrombocytopenia.

REFERENCES

1. Ruggeri ZM. Type IIB von Willebrand disease: A paradox explains how von Willebrand factor works. J Thromb Haemost. 2004;2(1):2-6.
2. Cooney KA, Nichols WC, Bruck ME, Bahou WF, Shapiro AD, Bowie EJ, et al. The molecular defect in type IIB von Willebrand disease. Identification of four potential missense mutations within the putative Gplb binding domain. J Clin Invest.1991;87(4):1227-1233.
3. Rayes J, Hollestelle MJ, Legendre P, Marx I, de Groot PG, Christophe OD, et al. Mutation and ADAMTS13-dependent modulation of disease severity in a mouse model for von Willebrand disease type 2B. Blood. 2010 Jun 10;115(23):4870-7.
4. Othman, Maha, and Emmanuel J. Favaloro. "Genetics of Type 2B von Willebrand Disease: 'True 2B,' 'Tricky 2B,' or 'Not 2B.' What Are the Modifiers of the Phenotype?" Seminars in Thrombosis and Hemostasis 34, no. 6 2008: 520-31. doi:10.1055/s-0028-1103363.
5. Federici AB, Mannucci PM, Stabile F, Canciani MT, Di Rocco N, Miyata S, et al. A type 2b von Willebrand disease mutation (Ile546-->Val) associated with an unusual phenotype. Thromb Haemost. 1997 Sep;78(3):1132-7.
6. Nurden P, Debili N, Vainchenker W, Bobe R, Bredoux R, Corvazier E, et al. Impaired megakaryocytopoiesis in type 2B von Willebrand disease with severe thrombocytopenia. Blood. 2006 Oct 15;108(8):2587-95.
7. Takimoto Y, Imanaka F. Type 2B Hiroshima: a variant of von Willebrand disease characterized by chronic thrombocytopenia and the presence of all von Willebrand factor multimers in plasma. Int J Hematol. 1999 Aug;70(2):127-31.
8. Smith LJ. Laboratory Diagnosis of von Willebrand Disease. American Society for Clinical Laboratory Science. 2017 Apr 1;30(2):65-74
9. Kruse-Jarres R, Johnsen JM. How I treat type 2B von Willebrand disease. Blood. 2018 Mar 22;131(12):1292-300.
10. Casonato A, Daidone V, Galletta E, Bertomoro A. Type 2B von Willebrand disease with or without large multimers: A distinction of the two sides of the disorder is long overdue. PLoS ONE. 2017;12(6):e0179566.
11. Rydz N, James PD. The evolution and value of bleeding assessment tools. J Thromb Haemost. 2012 Nov;10(11):2223-9.
12. Sadler JE, Mannucci PM, Berntorp E, Bochkov N, Boulyjenkov V, Ginsburg D, et al. Impact, diagnosis and treatment of von Willebrand disease. Thromb Haemost. 2000 Aug;84(2):160–74.
13. McGinnis E, Vercauteren SM. von Willebrand disease type 2B. Blood. 2017 Jan 26;129(4):538-538.
14. Ozeki M, Kunishima S, Kasahara K, Funato M, Teramoto T, Kaneko H, et al. A family having type 2B von Willebrand disease with an R1306W mutation: severe thrombocytopenia leads to the normalization of high molecular weight multimers. Thromb Res. 2010;125(2):e17-22.
15. Rick ME, Williams SB, Sacher RA, McKeown LP. Thrombocytopenia associated with pregnancy in a patient with type IIB von Willebrand's disease. Blood. 1987 Mar;69(3):786-9.
16. Federici AB, Mannucci PM, Castaman G, Baronciani L, Bucciarelli P, Canciani MT, Pecci A, Lenting PJ, De Groot PG. Clinical and molecular predictors of thrombocytopenia and risk of bleeding in patients with von Willebrand disease type 2B: a cohort study of 67 patients. Blood. 2009;113:526-534.
17. Weiss HJ, Sussman II. A new von Willebrand variant (type I, New York): increased ristocetin-induced platelet aggregation and plasma von Willebrand factor containing the full range of multimers. Blood. 1986 Jul;68(1):149-56.
18. HolmbergL, Dent JA, Schneppenheim R, Budde U, Ware J, Ruggeri ZM. von Willebrand factor mutation enhancing interaction with platelets in patients with normal multimeric structure.JClin Invest. 1993;91(5):2169-2177.