Received: 30 January 2019 | Revised: 20 February 2019 | Accepted: 23 February 2019

DOI: 10.1111/hae.13742

WILEY Haemophilia

LETTER TO THE EDITOR

Spontaneous recurrent intracranial haemorrhage in a woman with type 2B von Willebrand disease: A clinical case and a brief literature review

Von Willebrand disease (VWD) is an inherited bleeding disorder, caused by deficient or defective plasma von Willebrand factor (VWF), a large multimeric glycoprotein that plays a crucial role in platelet adhesion and aggregation, the main initial steps in haemostasis after vascular injury and stabilizing blood coagulation factor VIII (FVIII). It affects equally, males and females, with a frequency between 0.16% and 1 of the population. Three types of disease are recognized: (a) Type 1 VWD is a partial quantitative deficiency of VWF; (b) Type 2 VWD is characterized by a qualitative deficiency and defective VWF that includes four subtypes 2A, 2B, 2M and 2N; and (c) Type 3 VWD is a virtually complete quantitative deficiency of VWF; in this case, clinical manifestations are often similar to haemophilia. VWD type 2B includes qualitative variants with increased affinity for platelet GPIb. Patients with VWD type 2B often have variable thrombocytopenia that may be increased by use of desmopressin (DDAVP) or by stress. Patients with type 1 or 2 vWD usually have recurrent epistaxis, menorrhagia, mucocutaneous or postsurgical bleeding; while unlike haemophilia or type 3 VWD, haemarthroses are unusual. Intracranial haemorrhage (ICH) in von Willebrand patients is a very rare event.

We now report a clinical case of a women affected by VWD type 2B, who had presented two different episodes of spontaneous intracranial haemorrhages.

Our patient was hypothesized as being affected by a not specified coagulation disorder at 6 years of age, following recurrent and severe epistaxis, without a previous familial history for haemorrhagic diseases. She complained of menorrhagia during youth, and at 27 years of age, following a refractory postpartum haemorrhage she was subjected to a hysterectomy. Twenty years later, a bilateral oophorectomy was also performed when she reached early menopause, on the decision of the gynaecologists. The patient was initially treated on demand with plasma-derived products or red blood cells, and at 38 years of age, she developed a post-transfusion HCV-related liver disease. Our patient also suffered from an anxious-depressive syndrome and a poorly controlled arterial hypertension, treated with ramipril 2.5 mg/day. Until the age of 34 years, she had been a smoker (17 pack/year).

In 2004, at the age of 59 years, she was finally diagnosed with von Willebrand disease type 2B. Laboratory analyses showed the following: aPTT in normal range; FVIII:C 50.8 IU/dl (range 60–160 IU/dl); VWF:Ag 44.6 IU/dl (range 60–160 IU/dl; VWF:RCo 17.5 IU/dl (range 60–130 IU/dl); VWF:CBA 4IU/dl (range 65–150 IU/dl); VWF:FVIIIBA 36.9 IU/dl (range 65–150 IU/dl); Plt 135 × 10^3 μl (150–400 × 10^3 μl); the analysis of high molecular weight multimers was not performed. Genetic analysis revealed the presence of the c.3922C > T (p.Arg1308Cys) mutation. This disorder was also found in two brothers and one sister, who presented epistaxis, haematuria and severe postsurgical bleeding. No other concomitant coagulation disorder was found. The patient and her family members were put on-demand treatment with plasma-derived FVIII/VWF.

In July 2005, the patient was admitted to hospital for a sudden onset of cephalalgy and vomiting due to a right parieto-occipital intraparenchymal haematoma confirmed by CT scan. She immediately underwent neurosurgery to evacuate the haematoma; the intervention was performed under haemostatic coverage with plasma-derived FVIII/VWF concentrate (Haemate P®, CSL Behring GmbH, Germany) at dosage of FVIII 30 IU/kg/bid. The replacement treatment was continued for three days after surgery at dosage of 20 IU/Kg/bid, followed by 20 IU/Kg/day for a week, and by a long-term prophylaxis at dosage of 20 IU/Kg/tiw. A rehabilitation programme was started during this prophylactic therapy, but the patient continued to present left haemiparesis with homonymous haemianopsia. No other bleeding events were reported during the year in which our patient remained on prophylaxis with FVIII/VWF concentrate. Once the rehabilitation ended, the patient stopped the prophylactic treatment and we lost her to follow-up.

Twelve years later, in December 2017, she was again hospitalized for an ICH recurrence. The CT scan immediately performed showed the presence of a new right parieto-temporal haematoma, with intraventricular flooding (Figure 1). The patient died a short time after admission due to the severity of bleeding, and she had not been subjected to any haemostatic treatment.

Intracranial haemorrhages in VWD are a rare event that occurs in 2%–3.9% of patients[1,2] usually patients with VWD type 3, percentage similar to on-demand patients with haemophilia. Bleeding is often traumatic, especially in children, and occurs more easily in patients presenting severe disease, but also subjects with moderate or mild VWD are not protected from haemorrhagic events. To date, only a few cases of intracranial haemorrhages in VWD are reported in literature. Labarque et al,[1] in their retrospective study on 153 children, who had experienced head trauma, found six VWD patients with ICH, three had VWD type 3, one type 2A and two type 1; replacement therapy was used in four of them, while only one patient presented sequelae, a right-sided haemiplegia. In the Lak et al study

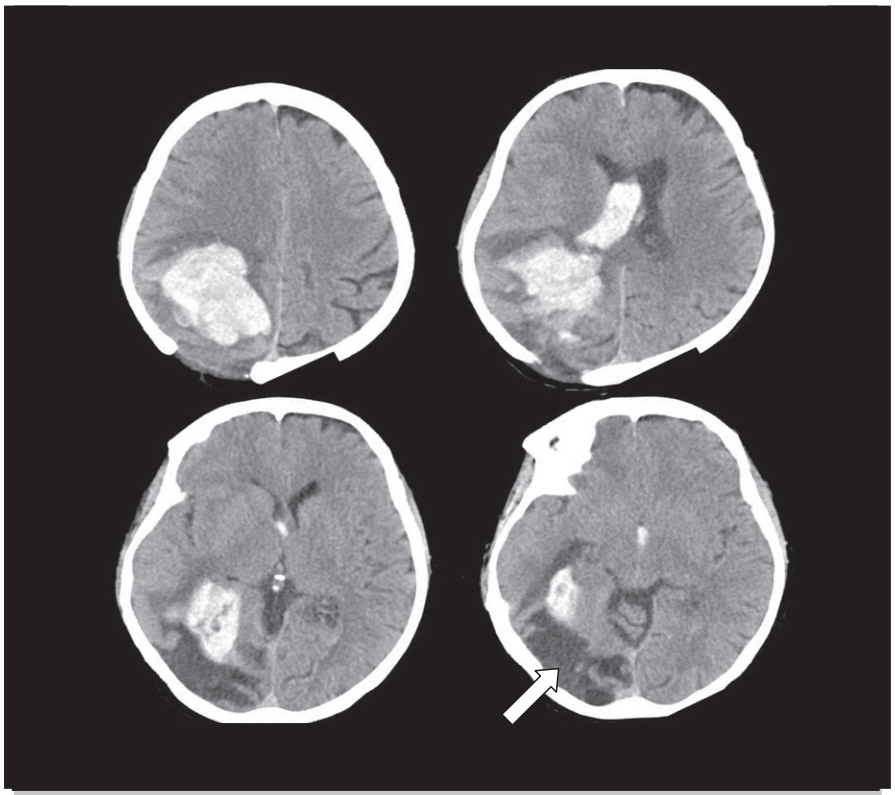

FIGURE 1 CT scan for recurrent intracranial haemorrhage presented: *New right parieto-temporal haematoma, with intra-ventricular flooding. Lower degenerative atrophic area (withe arrow), outcome of previous haematoma of 2005*

on 385 Iranian patients with type 3 VWD,[2] seven cases of ICH were reported, with an overall prevalence of ICH (2%) similar to that of on-demand patients with haemophilia.[3] Five other manuscripts were published in 25 years, from 1985 to 2010,[3-7] reporting a total of 9 ICH in VWD; 67% of these patients were treated with replacement therapy for a period between 3 and 10 days, while for three patients no data about treatment were available. A different choice of therapy was performed: Luongo et al[8] had treated their type 1 VWD patient, presenting bilateral chronic spontaneous haematoma, with desmopressin, whereas Osenbach et al[9] used the cryoprecipitate to treat a young girl with intraventricular haemorrhage secondary to a ruptured of an arteriovenous malformation. About half of the reported cases were traumatic, and two were due to cerebral malformations or thrombosis, while those remaining were spontaneous ICH. Long-term prophylaxis with replacement therapy was established only for three children,[2] all presenting a severe type 3 VWD. All these cases are displayed in Table 1.

This brief review of the literature, which revealed a small number of reported cases, shows a lack of uniformity in the management of patients with VWD who had an ICH.

Our patient had a type 2 B VWD, diagnosed in adulthood. Before the first ICH, she had had no bleeding episodes that would have required long-term treatment. In her case, ICH was a spontaneous and sudden event that required hospitalization and surgery in addition to haemostatic treatment.

Surgery in patients with VWD type 2 variants may be extremely difficult and should be carried out in a centre where there are specialists in coagulation diseases. In case of major surgery, the UKHCDO Guidelines[10] recommend a pre-operative correction of both VWF:RCo and FVIII (≥ 100 IU/dl) with DDAVP or FVIII/VWF concentrate. Our patient was treated with a plasma-derived concentrate before the emergency neurosurgery, while desmopressin was contraindicated due to usually poor therapeutic response and to increased risk of thrombocytopenia that occurs in the type 2B variant. A short-term prophylaxis for 6–10 days with the same product used for surgery is recommended to maintain both VWF:RCo and FVIII > 50 IU/dl. In our case, the patient was postoperatively treated with FVIII/VWF initially for 10 days, followed by a prophylactic treatment lasting one year with a reduced dose of replacement concentrate. The protective role of early prophylaxis in haemophilia patients has been recently reported by Andersson et al[11] and confirms the recommendations from international guidelines on haemophilia management.[12] Primary prophylaxis is always recommended in cases of severe haemophilia, but a secondary prophylaxis should be strongly considered also in cases of mild patients following a first severe event or recurrent bleeds. To date, a prophylaxis is rarely indicated in patients with VWD; in fact, they had often a mild disease, and spontaneous bleeds were not frequent. Long-term regular prophylaxis is usually prescribed only in cases of severe VWD type 3 presenting haemarthroses, epistaxis, menorrhagia or gastrointestinal bleeding due to angiodysplasia. Despite the low use of prophylaxis habitually performed, the recent international guidelines recommend a long-term prophylaxis in all types of VWD patients with recurrent bleeding,[10] as suggested in case of mild haemophilia patients. Our patient presented recurrent severe epistaxis and menorrhagia

TABLE 1 Summary of published reports on intracranial haemorrhage in von Willebrand Disease (vWD) from 1985 to today

Author and year	Patients no (sex)	Age (years)	Type of haemorrhage	Type of vWD	Treatment	Dose and duration of haemostatic treatment	Haemorrhagic complications
Labarque V, et al; 2013[2]	6 (4M/2F)	Median 2.9	Traumatic intracerebral haemorrhage	vWD type 3	FVIII bolus injection	NS dose for long-term prophylaxis	Right-sided haemiplegia
			Traumatic subdural haematoma	vWD type 1	None		None
			Traumatic posterior fossa haemorrhage	vWD type 3	Intensive replacement treatment	NS dose for long-term prophylaxis	None
			Traumatic subdural haematoma	vWD type 3	Intensive replacement treatment	NS dose for long-term prophylaxis	None
			Traumatic subdural haematoma	vWD type 2N	None		None
			Traumatic chorioid plexus haemorrhage	vWD type 1	Intensive replacement treatment	NS dose for two weeks	None
Luongo M, et al; 2012[8]	1(/)	NA	Bilateral chronic spontaneous haematoma	vWD type I	DDAVP	NA	None
Mishra P, et al; 2008[7]	1 (/)	NS (Median in study 8.0)	Intracranial haemorrhage	vWD type 3	Replacement therapy	10 days	NA
Wetzstein V, et al; 2006[6]	1 (M)	0	Large right temporal subdural haematoma, and large bleeding site in the right posterior cranium subsequent sinus vein thrombosis	vWD type 3	FVIII/vWF infusion	NA	None
Nakau R, et al; 2005[5]	1(F)	59	Intracerebral haemorrhage in the right lobe	vWD type 2A	Surgery and bolus injection FVIII/vWF	2000 UI before surgery, followed by 2000 UI/day for three days	None
Lak M, et al; 2000[2]	7 (/)	NA	NS central nervous system bleeding	vWD type 3	NS replacement therapy	NS dose for 3-4 days	NA
Mullaart RA, et al; 1991[3]	1 (F)	0	Periventricular haemorrhage	vWD type 2A			
Osenbach RK, et al; 1989[9]	1 (F)	13	Intraventricular haemorrhage secondary to ruptured arteriovenous malformation	vWD type 1	Cryoprecipitate bolus injection, followed by continuous infusion of cryoprecipitate and surgery	NS dose for 14 days	None
Almaani WS & Awidi AS; 1986[4]	4 (2M/2F)	18-22-23; 65	3 intracranial haemorrhage 1 intraventricular haemorrhage	NS vWD	Replacement therapy	NA	NA

0: newborn; AVM: arteriovenous malformation; DDAVP: desmopressin; FVIII: coagulation factor VIII; NA: not Available; NS: Not specified; vWD, von Willebrand Disease; vWF, von Willebrand factor

during childhood and youth, and all treated on demand with red blood cells or plasma-derived products. After the first episode of ICH, a prophylaxis was started to prevent recurrence, but it was interrupted one year later as the patient had ended the physiotherapy and there were no clear indications or guidelines to establish the duration of the treatment.

A known risk factor for ICH in haemophilia patients is hypertension, often not properly treated or controlled; also our patient was affected by this clinical condition; and similarly to that reported in cases of people with haemophilia, she also did not comply with the medication prescribed.

Based on our case report and on this brief review of literature, ICH in VWD patients is not frequently reported, and its management is often difficult and not well standardized. Similarly to haemophilia, a long-term prophylaxis with replacement concentrate could reduce the risk of a recurrence, and sometimes fatal bleeding. Hypertension should be well monitored as it is one of the major risk factors for ICH.

Studies and registries would be very important to define the burden of ICH in VWD patients clearly and establish its proper management.

ACKNOWLEDGEMENTS

Z.E. and P.S. analysed the data and wrote the paper, M.R. performed all neuroradiological analysis, all the authors have given final approval of the version to be published. All of the authors meet the International Committee of Medical Journal Editors criteria for authorship for this manuscript, have taken responsibility for the integrity of the work as a whole, and have given final approval of the version to be published.

DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

ORCID

Ezio Zanon https://orcid.org/0000-0001-6149-1155
Samantha Pasca https://orcid.org/0000-0002-0954-013X

Ezio Zanon[1]
Samantha Pasca[1]
Antonella Bertomoro[2]
Rodica Mardari[2]
Paolo Simioni[1]

[1]*Department of Medicine, Haemophilia Centre, University Hospital of Padua, Padua, Italy*
[2]*Department of Neuroradiology, University Hospital of Padua, Padua, Italy*

Correspondence
Ezio Zanon, Haemophilia Centre, Department of Medicine, University Hospital of Padua, Padua, Italy.
Email: zanezio61@gmail.com

REFERENCES

1. Labarque V, Stain AM, Blanchette V, et al. Intracranial haemorrhage in von Willebrand disease: a report on six cases. *Haemophilia*. 2013;19(4):602-606.
2. Lak M, Peyvandi F, Mannucci PM. Clinical manifestations and complications of childbirth and replacement therapy in 385 Iranian patients with type 3 von Willebrand disease. *Br J Haematol*. 2000;111:1236-1239.
3. Almaani WS, Awidi AS. Spontaneous intracranial hemorrhage secondary to von Willebrand's disease. *Surg Neurol*. 1986;26(5):457-460.
4. Mullaart RA, Van Dongen P, Gabreëls FJ, van Oostrom C. Fetal periventricular hemorrhage in von Willebrand's disease: short review and first case presentation. *Am J Perinatol*. 1991;8(3):190-192.
5. Nakau R, Nomura M, Kida S, et al. Subarachnoid hemorrhage associated with von Willebrand's disease-case report. *Neurol Med Chir (Tokyo)*. 2005;45(12):631-634.
6. Wetzstein V, Budde U, Oyen F, et al. Intracranial hemorrhage in a term newborn with severe von Willebrand disease type 3 associated with sinus venous thrombosis. *Haematologica*. 2006; 91 (12 Suppl): ECR6.
7. Mishra P, Nithani R, Dolai T, et al. Intracranial haemorrhage in patients with congenital haemostatic defects. *Haemophilia*. 2008;14(5):952-955.
8. Luongo M, Pizzuti M, Godano U. Bilateral chronic subdural nontraumatic hematoma associated with Von Willebrand's type I disease: a case report. *Acta Neurochir*. 2012;154:1087-1088.
9. Osenbach RK, Loftus CM, Menezes AH, et al. Management of intraventricular haemorrhage secondary to ruptured arteriovenous malformation in a child with von Willebrand's disease. *J Neurol Neurosurg Psychiatry*. 1989;52(12):1452-1454.
10. Laffan MA, Lester W, O'Donnell JS, et al. The diagnosis and management of von Willebrand disease: A United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *Br J Haematol*. 2014;167(4):453-465.
11. Andersson NG, Auerswald G, Barnes C, et al. Intracranial haemorrhage in children and adolescents with severe haemophilia A or B - the impact of prophylactic treatment. *Br J Haematol*. 2017;179:298-307.
12. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Treatment guidelines working group on behalf of the world federation of Hemophilia. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1-47.