Successful management of multiple pregnancies in a family with varying severity of Von Willebrand disease

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Abstract

We present the obstetric history of a family of three sisters with Von Willebrand disease, managed in our centre over the course of nine successful pregnancies. The abnormalities result from inheritance of an exon 50 skipping mutation in the Von Willebrand factor gene, resulting from consanguinity. Two of the sisters were identified as having a severe phenotype with a Von Willebrand factor level of less than 5 IU/dl, with the other having a mild phenotype. Of the sisters with a severe phenotype, one had a number of prenatal complications and required early onset prophylaxis with Von Willebrand factor concentrate, whilst the other had a less complicated clinical course, only requiring Von Willebrand factor concentrate to cover labour. The sister with mild Von Willebrand disease had a rise in Von Willebrand factor levels during pregnancy and required no specialist treatment. The report highlights the markedly different clinical courses that can occur in patients with Von Willebrand disease and the different approaches to management.

Keywords

Clinical genetics, haematology, haemorrhage, Von Willebrand disease

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Introduction

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, with the estimated prevalence ranging from 0.3 to 1.3%.¹ Von Willebrand factor (VWF) plays a critical role in both primary and secondary haemostatic functions, through facilitating platelet adhesion and acting as a carrier molecule for Factor VIII. VWD is a heterogeneous condition, which is autosomally inherited, in either a dominant or recessive pattern. It is broadly categorised as type 1, in which there is a mild quantitative deficiency in VWF; type 2, in which there is a dysfunctional form of VWF; and type 3, in which there is a severe quantitative deficiency.² This case study considers a family with both mild and severe deficiencies, resulting from the inheritance of a pathogenic *VWF* variant on either 1 or 2 alleles.

Three affected members of the family were managed successfully in our centre over the course of nine pregnancies. The abnormalities result from inheritance of an exon 50 skipping mutation in the *VWF* gene, resulting from consanguinity. Two sisters presented in childhood and were identified as having severe disease with VWF ristocetin co-factor assay (VWF:RCO) of less than 5 IU/dl. Two other sisters were subsequently investigated. One was found to have a mild phenotype and the other normal VWF levels.

Clinical and phenotypic data

Case 1 has a diagnosis of type 3 VWD. In her first pregnancy, she proceeded to a spontaneous vaginal delivery at term but developed a post-partum haemorrhage (PPH) estimated at 1000 ml, requiring a two unit packed red cell transfusion. Examination under anaesthetic identified a small vaginal tear. She was managed with twice daily Haemate P, an intermediate purity VWF concentrate containing both VWF and

Factor VIII (FVIII), during labour and on the following day. Subsequently, she was given alternate day VWF concentrate replacement for 5 weeks because of ongoing intermittent bleeding, aiming to keep FVIII and VWF:RCO both greater than 50 IU/dl. The persistent bleeding was eventually found to be due to endometritis and settled with a course of broad spectrum antibiotics (Table 1).

In her second pregnancy, an initial fetal ultrasound scan, performed at 26 weeks gestation, showed large placental lakes involving most of the peripheral aspects of the placenta. In view of this unusual appearance, she was given prophylaxis with VWF concentrate three times weekly until the conclusion of the pregnancy, as it was considered she may be at risk of subchorionic haemorrhage. Serial ultrasound scans performed at weekly intervals showed improvement through the pregnancy, suggesting a response to VWF replacement. At delivery, placental histology was reviewed and confirmed subchorionic fibrin deposition, with some intervillous haemorrhage. Otherwise no abnormality was identified on macroscopic and

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microscopic examination. This child was also born via spontaneous vaginal delivery at 39 weeks, with delivery again covered with twice daily VWF concentrate, this time for 3 days. This was reduced to twice weekly prophylaxis after discharge for 6 weeks.

During her third pregnancy, despite normal ultrasound scan appearances, prophylaxis with VWF concentrate was instituted from 20 weeks and continued until term in view of the large placental lakes that were identified during the previous pregnancy. Haemate P was administered at a dose of 2000 IU on alternate days, aiming to maintain VWF:RCO greater than 20 IU/dl. Her third child was born via an induced delivery at 41 weeks gestation, with VWF concentrate to cover labour. There was an estimated postpartum blood loss of 350 ml. She continued to have intermittent minor bleeding for a period of around 6 weeks and required alternate day VWF factor concentrate to control this.

Case 2 also has a diagnosis of type 3 VWD. She first became pregnant at 19 years of age, with no rise in VWF levels observed during pregnancy. Ante-partum care was uncomplicated and she had a normal vaginal delivery, which was covered with VWF concentrate at onset of labour and 12 h afterwards. An episiotomy was required and there was an estimated PPH of 850 ml. She continued with VWF concentrate for 3 days achieving good haemostatic control. Two subsequent pregnancies followed an uncomplicated antenatal course. In each case labour was covered with VWF concentrate, with twice daily administration for 3 days post-partum, with close laboratory monitoring of VWF and Factor VIII levels to guide dosage. No significant bleeding complications were noted.

In all deliveries, regional anaesthesia (spinal or epidural) and fetal scalp monitoring were avoided to minimise risk to the neonate.

Case 3 has a diagnosis of type I VWD and has completed three pregnancies, none of which required specialist treatment. All were monitored closely during pregnancy, particularly in the immediate post-natal period. There was an observed rise in VWF levels in each pregnancy to within normal levels.

Genetics

Sequencing of all 52 exons of the *VWF* gene identified a previously unreported c.8155 + 6T > A substitution. It was confirmed that this abnormality segregated with the disease, with the type 3 individuals being homozygous for the variant, and those with mild symptoms having a heterozygous genotype. The effect of this variant was elucidated by RNA analysis, which revealed that exon 50 is spliced out of the mRNA. Exon 50 lies within the CK domain, which comprises the last 150 amino acids of the mature VWF protein. These are essential for the dimerisation of the VWF subunits, which occurs within the endoplasmic reticulum and is a vital precursor to multimer formation in the Golgi apparatus. Prevention of dimerisation of VWF results in a significant loss of VWF haemostatic function and a rapid clearance of VWF from the circulation.

Management of VWD in pregnancy

Management of VWD in pregnancy can be complex and requires a multidisciplinary approach, with close liaison between obstetricians, haematologists, anaesthetists, the midwifery team and the laboratory. It is generally accepted that most women with VWD can undergo normal vaginal delivery, with Caesarean section being reserved for standard obstetric indications. Caution regarding delivery of the fetus must be exercised in view of the high risk of the fetus also being affected, and as such instrumentation at delivery and fetal scalp monitoring should be avoided.³ Genetic counselling should be offered in the antenatal setting to affected women, to discuss the inheritance of the condition.⁴ However, due to the complexity of the *VWF* gene a causative mutation is not always identified making prenatal diagnosis challenging.

The above cases highlight the variation in management that is seen between patients with VWD. The majority of patients with type 1 VWD will experience a transient rise in VWF levels during pregnancy. It is important to check VWF levels in the third trimester to confirm that there has been a rise in levels and allow for a delivery plan to be formulated.⁵ Patients with type 3 VWD rarely demonstrate a rise in VWF levels and as such will require VWF concentrate to minimise bleeding risks in the perinatal period. Expert consensus is that one should aim to achieve VWF:RCO and FVIII levels of greater than 50 IU/dl prior to delivery and that this should be maintained for 3–5 days, depending on the individualised risk for PPH.^{6,7}

A few published case series detail the management of pregnancy in women with VWD. Lak et al. reported on 100 pregnant women with type 3 vWD managed in Iran.⁸ No patients were given prophylactic treatment prior to onset of labour, with labour managed with either cryoprecipitate, fresh frozen plasma or FVIII concentrates. They reported a 15% incidence of PPH in their patient group. Kadir et al. reported a similar incidence of primary PPH, with 18.5% affected from 54 pregnancies; however, their patients had varying severities of VWD, and none of those who received prophylactic treatment in labour had any reported bleeding complications.⁹ They also reported an incidence of secondary PPH, occurring 24 h after delivery, of 20%. Finally, Ramsahoye et al. reported an incidence of primary PPH of 12.5% and secondary PPH of 25% from a total of 24 pregnancies with varying severities of VWD.¹⁰ Of their patient group, 19 had a normal vaginal delivery and 5 had Caesarean section, with all of the latter covered with either VWF concentrate, cryoprecipitate or in one case DDAVP.

In non-severe VWD, VWF levels generally fall quickly in the post-partum period, with one study showing a significant drop from 7 days post-partum.¹¹ As a result of this, there is an increased risk of late PPH, with between 25 and 50% of women with VWD estimated to be affected.¹² The average time of presentation with PPH has been estimated to be 15.7 ± 5.2 days from delivery, highlighting the importance of close contact with these patients in the immediate post-natal period.¹³ Reassuringly, it has been shown that other adverse outcomes such as premature labour, placental abruption, fetal growth restriction

Table 1. Clinical and genetic familial characteristics.

	VIIIc	VWF:Ag	VWF:RCO	Clinical presentation	VWF genotype
Mother	97.6	43.0	42	Mild	Heterozygous c.8155 + 6T > A
Father	116.8	47.2	41.1	Mild	Heterozygous c.8155 + 6T > A
1	1.9	1.7	<5	Severe	Homozygous c.8155 + 6T > A
2	2.2	1.1	<5	Severe	Homozygous c.8155 + 6T > A
3	115.2	55.7	37.3	Mild	Heterozygous c.8155 + 6T > A
4	120.1	119.9	88	Normal	c.8155 + 6T

or intrauterine fetal demise are not increased in VWD patients compared with the general population.¹²

Other treatment options in VWD include DDAVP, although caution must be exercised in view of potential risks of fluid overload and thromboembolism, which are heightened in the perinatal period. Antifibrinolytics, such as tranexamic acid, can be very useful as a supportive treatment and as an adjunct to VWF concentrate in those with more severe disease. Epidural or spinal anaesthesia can be used if it is clear that there is no coagulation defect however should be avoided if there are any doubts around this.

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References

1. Keeney S and Cumming A. The molecular basis of von Willebrand Disease. *Clin Lab Haematol* 2001; 23: 209–230.
2. Sadler J and Budde U. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. *J Thromb Haemost* 2006; 4: 2103–2114.
3. Demers C and Derzko C. Gynaecological and obstetric management of women with inherited bleeding disorders. *J Obstet Gynaecol Can* 2005; 27: 707–732.
4. Kadir R. Women and inherited bleeding disorders: pregnancy and delivery. *Semin Hematol* 1999; 36: 28–35.
5. Kouides PA. Obstetric gynaecological aspects of von Willebrand's disease. *Best Pract Res Clin Haematol*. 2001; 14: 381–399.
6. Pasi KJ and Collins PW. Management of von Willebrand's disease; a guideline from UKHCDO. *Haemophilia* 2004; 10: 218–231.
7. Manucci PM. Treatment of Von Willebrand's disease. *New Engl J Med* 2004; 352: 683–694.
8. Lak M and Peyvandi F. Clinical manifestations and complications of childbirth and replacement therapy in 385 Iranian patients with type 3 von Willebrand's disease. *Br J Haematol* 2000; 111: 1236–1239.
9. Kadir RA and Lee CA. Pregnancy in women with von Willebrand's disease or factor XI deficiency. *Bjog: Int J O&G* 1998; 105: 314–321.
10. Ramsahoye BH and Davies SV. Obstetric management in von Willebrand's disease: a report of 24 pregnancies and a review of the literature. *Haemophilia* 1995; 1: 140–144.
11. Sánchez-Luceros A and Meschengieser SS. Factor VIII and von Willebrand factor changes during normal pregnancy and puerperium. *Blood Coagul Fibrinolysis* 2003; 14: 647–651.
12. James AH and Jamison MG. Bleeding events and other complications during pregnancy and childbirth in women with von Willebrand disease. *J Thromb Haemost* 2007; 5: 1165–1169.
13. Roque H and Funai E. von Willebrand disease and pregnancy. *J Matern Fetal Med* 2000; 9: 257–266.