CLINICAL VIGNETTE

Management of Von Willebrand Disease in Labor and Delivery

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Introduction

Von Willebrand disease (vWD) is an inherited bleeding disorder of von Willebrand factor (vWF) causing decreased platelet binding. In the laboring patient, this may predispose to postpartum hemorrhage or bleeding after neuraxial anesthesia, possibly leading to an epidural hematoma. Furthermore, changes that can occur naturally in the coagulation system during pregnancy may complicate diagnosis and treatment. This case report illustrates the management of a pregnant woman presenting to labor and delivery with a history of easy and frequent bleeding.

Case Report

The patient is a 32-year-old nulliparous female with a singleton gestation. During prenatal visits, she reported a history of heavy menstruation, prolonged mucocutaneous bleeding after injury, and frequent epistaxis, as well as a family history of a bleeding disorder. She otherwise had stable mild, intermittent asthma and did not take any medications increasing her bleeding risk. She underwent laboratory testing showing a normal platetlet count, vWF:Ag level of 22%, vWF:Ristocetin cofactor (RCo) activity level of 14%, and Factor VIII (FVIII) activity of 26%. Given the ratio of the activity level to protein level (vWF:RCo to vWF:Ag) was less than 0.7 with a loss of large vWF multimers on analysis, she was presumed to have type 2A vWD.

She presented to the hospital at 30 weeks gestation due to three days of increasing pelvic pressure. Fetal heart tone monitoring, noted intermittent late decelerations, and she was admitted for continuous fetal monitoring. After several days of inpatient fetal monitoring, she had a prolonged, severe fetal heart rate deceleration, prompting emergent cesarean section. Given the need for a rapid delivery, the anesthesiologist administered general anesthesia instead of neuraxial anesthesia. She was given 5200 U, or 60 U/kg, of Alphanate, a plasma-derived vWF and FVIII concentrate, as well as 1 gm of intravenous tranexamic acid at the start of surgery. Estimated blood loss during the case was 900 mL, which is an average amount for a cesarean delivery.

Postoperatively, she had daily laboratory checks of her vWF:Ag and FVIII levels and was continued on 20 U/kg of Alphanate every 8 hours for 3 days postoperatively. She then received oral tranexamic acid 25 mg/kg 3 times daily for 10 days. On the second postoperative day, her vWF:Ag levels increased above 200% prompting a decrease in Alphanate dosing to once daily. She had no significant bleeding episodes during her post-operative period.

Discussion

Von Willebrand disease has a reported prevalence of 1.3% based on testing and survey of 600 ethnically diverse school-children, though the prevalence is lower when considering only those with symptomatic bleeding.[1] The disease results from a deficiency in vWF, a glycoprotein that forms large multimers which is synthesized in endothelial cells and megakaryocytes. The glycoprotein mediates platelet adhesion to sites of injury and acts as a chaperone and stabilizer to FVIII.

There are three types of vWD depending on the type of deficiency present. Type I vWD results from a quantitative reduction in vWF. It is the most common type with variable degrees of decreased vWF, generally 5 to 30% of normal. Type 2 vWD occurs from dysfunctional protein with various subtypes. For example, in Type 2A, there is a decrease in the formation of larger, more effective vWF multimer proteins through a variety of possible gene mutations. In Type 2B, there is increased platelet binding to vWF with accelerated platelet clearance and thrombocytopenia, as well as a loss of the larger vWF multimers. In Type 2N, there is reduced binding of FVIII, resulting in low FVIII levels and a presentation similar to hemophilia A. There is a severe deficiency or absence of vWF in Type 3 disease, characterized by the earliest and heaviest signs of bleeding.

Assessment in the pregnant population is complicated by the natural increase in vWF due to estrogen, which results in increased vWF levels up to three times normal.[2] However, women with mild vWD had excessive bleeding documented in 8 out of 38 deliveries despite an increase in vWF from low to within normal range by the third trimester.[3] In this case, the patient displayed low levels of both vWF and vWF binding activity to the platelet membrane receptor GPIb, as measured by the vWF:RCo assay. Given that the binding activity was lowered by a greater degree than the protein level (vWF:Ag), the laboratory values reflect a qualitative, more than quantitative deficiency in vWF. The loss of large multimers favors a diagnosis of Type 2A vWD. There were no laboratory measurements from earlier in the pregnancy to assess the trajectory of coagulation changes.

Treatment of vWD includes a variety of hemostatic agents including antifibrinolytic agents, such as tranexamic acid; desmopressin, except in cases when it may exacerbate thrombocytopenia as in Type 2B; and vWF concentrates, either plasma-derived or recombinant. The plasma-derived concentrates have variable amounts of FVIII depending on the manufacturer. All of these treatment forms may be used during delivery or the postpartum period depending on the type of vWD and risk for bleeding.

The American Society of Hematology, the International Society on Thrombosis and Haemostasis, the National Hemophilia Foundation, and the World Federation of Hemophilia have published guidelines regarding the management of vWD, including for neuraxial anesthesia during labor.[4] The guidelines recommend targeting and maintaining vWF activity level of 0.50 to 1.50 IU/mL for placement of a neuraxial anesthetic and for at least 6 hours after removal of the epidural catheter. For major surgery, such as a cesarean delivery, the guidelines recommend maintaining levels of both FVIII and vWF above 0.50 IU/mL for at least three days. Additionally, for the postpartum period, use of the antifibrinolytic medication tranexamic acid is suggested, especially in patients with Type I vWD, to reduce the risk of postpartum hemorrhage.

A retrospective analysis of 106 cesarean and vaginal deliveries in patients with vWD described the treatments, use of neuraxial anesthesia, and outcomes for these cases.[5] Neuraxial anesthesia was administer in 94 (88.7%) deliveries, with pretreatment with desmopressin or vWD/FVIII concentrate prior to the procedure done in 21.8% of type I vWD cases, 71.4% of type 2 vWD cases, and 25% of unknown type cases. No adverse effects, including hematoma or thromboembolism, occurred from neuraxial anesthesia. Postpartum hemorrhage occurred in 10.4% of deliveries.

Given the relatively high prevalence of vWD, appropriate diagnosis and treatment in the laboring patient is critical. Consensus guidelines for the management of vWD in the context of labor and delivery have been developed with key recommendations. Clinical experience has demonstrated safe outcomes for delivery and neuraxial anesthesia, especially when hemostatic treatments have been administered.

REFERENCES

1. **Werner EJ, Broxson EH, Tucker EL, Giroux DS, Shults J, Abshire TC**. Prevalence of von Willebrand disease in children: a multiethnic study. *J Pediatr*. 1993 Dec;123(6):893-8. doi: 10.1016/s0022-3476(05)80384-1. PMID: 8229521.
2. **Lipe BC, Dumas MA, Ornstein DL**. Von Willebrand disease in pregnancy. *Hematol Oncol Clin North Am*. 2011 Apr;25(2):335-58, viii. doi: 10.1016/j.hoc.2011.01.006. PMID: 21444034.
3. **Lavin M, Aguila S, Dalton N, Nolan M, Byrne M, Ryan K, White B, O'Connell NM, O'Sullivan JM, Di Paola J, James PD, O'Donnell JS**. Significant gynecological bleeding in women with low von Willebrand factor levels. *Blood Adv*. 2018 Jul 24;2(14):1784-1791. doi: 10.1182/bloodadvances.2018017418. PMID: 30042144; PMCID: PMC6058240.
4. **Connell NT, Flood VH, Brignardello-Petersen R, Abdul-Kadir R, Arapshian A, Couper S, Grow JM, Kouides P, Laffan M, Lavin M, Leebeek FWG, O'Brien SH, Ozelo MC, Tosetto A, Weyand AC, James PD, Kalot MA, Husainat N, Mustafa RA**. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Adv*. 2021 Jan 12;5(1):301-325. doi: 10.1182/bloodadvances.2020003264. PMID: 33570647; PMCID: PMC7805326.
5. **Reale SC, Farber MK, Lumbreras-Marquez MI, Connors JM, Carabuena JM**. Anesthetic Management of Von Willebrand Disease in Pregnancy: A Retrospective Analysis of a Large Case Series. *Anesth Analg*. 2021 Nov 1;133(5):1244-1250. doi: 10.1213/ANE.0000000000005502. PMID: 33913917.