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Postpartum Hemorrhage Resulting From Inherited and/ or Acquired Von Willebrand Factor Deficiency – Own Experience and Review of Literature

KEYWORDS: postpartum hemorrhage, bleeding, von Willebrand disease.

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ABSTRACT *Inherited and acquired forms of von Willebrand factor (vWF) deficiency, referred to as von Willebrand disease and syndrome, respectively, belong to the most frequent bleeding disorders. We present a case of previously undetected Willebrand disease/syndrome which manifested in pregnant woman after otherwise uncomplicated cesarean delivery. In the hereby described case, the deficiency of vWF was accompanied by autoimmune hypothyroidism. Administration of FFP, cryoprecipitate and recombinant factor VIIa caused transient normalization of hemostasis in our patient. However, despite the normalization of thyroid function we did not achieve a persistent increase in vWF levels of our patient. Therefore, the patient was referred for further specialist evaluation and treatment at the tertiary center.*

Introduction

There are multiple reports of women with von Willebrand disease (vWD) who have experienced bleeding complications during pregnancy [1-5]. Despite the primary role of uterine contractions in controlling bleeding at the time of delivery, women with vWD are at an increased risk of postpartum hemorrhage. There are no data on the frequency of the diagnosis of vWD among women giving birth and only limited data on the incidence of bleeding events and other complications that women with vWD experience during pregnancy and childbirth.

VWD is one of the most common bleeding disorders. It results from impaired structure, function, synthesis or release of adhesion plasma glycoprotein, referred to as von Willebrand factor (vWF). vWF is synthesized by vascular endothelial cells and, to a lesser extent, by megakaryocytes of the bone marrow. Furthermore, vWF was shown to be involved in platelet aggregation and formation of a clot. As a result of an interaction between vWF and subendothelium, factor VIII can be transported directly to the site of vascular injury with resultant relative increase in its concentration [2].

Inherited form of vWD constitutes the most frequent type of bleeding disorder. Its incidence is estimated at 1 per 1000 irrespective of sex. There are three main types of inherited vWD: type 1 (mild, quantitative), type 2 (qualitative) and type 3 (severe, complete lack of vWF) [3,4]. vWD results in a mixed type, platelet and plasma, bleeding disorder. The symptoms may vary depending on a disease type, and their severity is to a large extent determined by the activity of vWF. Diagnosis of vWD is usually challenging as basic parameters of hemostasis are normal in most cases. Type 1 is the most prevalent form of vWD, diagnosed in 60-80% of the cases. Patients suffering from this type of vWD present with decreased plasma activity and concentration of vWF. Although the symptoms are usually mild and include small bruises, epistaxis, gingival bleeding and heavy, prolonged periods in female patients, also severe hemorrhages were sporadically reported in patients with type 1 vWD. Also traumas and surgical injuries may result in severe bleeding, even in the case of mild asymptomatic vWD. Despite available treatment, also acquired form of vWD is increasingly reported as a significant clinical problem.

We present a case of previously undetected Willebrand disease/syndrome which manifested in pregnant woman after otherwise uncomplicated cesarean delivery.

Case presentation

A 31-year-old woman (2nd pregnancy, 1st labor, 40th week of gestation) was admitted due to labor to our obstetrics clinic. The patient had about two-year history of anti-hypothyroid treatment, and irregularly took L-thyroxin (50 µg per day) during three months prior to the hospitalization. The results of functional thyroid tests, conducted 8 weeks before the admission, were normal. Due to the risk of fetal asphyxia, manifested as severe late decelerations on cardiotocography, the patient was qualified to a selective cesarean delivery on an emergency basis. She had the history of strabismus surgery at the age of five years, and uterine evacuation due to miscarriage at the 10th week of previous pregnancy. No anesthetic perioperative complications were recorded during both the procedures. Prior to conception, the patient had regular 28-day-long cycles, with 4-day-long menses of moderate severity.

The cesarean delivery was performed under spinal anesthesia. Male newborn (3630 gram, Apgar scores 9-10-10 points) was delivered. As uterine hypotonia was documented in the course of the cesarean section, dinoprost (Sanofi Synthelabo, Hungary) was administered in intravenous infusion, along with 20 units of oxytocin (Grindex, Latvia) and 0.2 mg of methylergometrine (Spofa Praha, Czech Republic), under continuous monitoring of uterine contractions. Reduced severity of bleeding enabled application of multiple hemostatic sutures onto the myometrium, hemostasis, and completion of the procedure. Coagulation profile and complete blood count were normal. The patient, in good general and local status and without any complications, was discharged home on postoperative day 3, with control visit scheduled after four weeks.

However, four weeks after the cesarean delivery, the patient was re-admitted on an emergency basis due to heavy vaginal bleeding. She had anemia (hemoglobin 8.9 g/dl, norm: 12.0-16.0 g/dl, hematocrit 27%, norm: 36.0-50.0%), slightly prolonged activated partial thromboplastin time (APTT, 37 s, norm: 28-36 s), and borderline time of bleeding (8 min, norm <8 min). The arterial blood pres-

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sure amounted to 70/0 mmHg, and heart rate (HR) to 130 beats per min. A speculum exam revealed about 1200 ml of clotted blood in the vagina. Extensive fluid resuscitation was implemented due to severe hypovolemia, and the patient was transferred to the surgical block on an emergency basis. An instrumental control of the uterine cavity was performed under endotracheal anesthesia, and hemostatic sutures were placed onto the rupture of the vaginal fornix. Recombinant factor VIIa (4.0 mg, NovoSeven, Novo Nordisk A/S, Denmark) was administered intravenously due to persistent severe vaginal hemorrhage, resulting in the control of bleeding 15 minutes thereafter. Overall, 4 units of erythrocyte concentrate, 3 units of fresh frozen plasma (FFP), 6 units of cryoprecipitate (CPAG), and 500 ml of colloids (6% HES) were transfused intraoperatively. Further management included normalization with colloid and crystalloid solutions, as well as the control of circulatory parameters and overall balance of fluids. As the general status of the patient improved systematically, she was transferred to the Department of Obstetrics, and subsequently discharged home in good general status on postoperative day 4.

Two weeks after the discharge the patient was readmitted to the clinic on an emergency basis due to massive vaginal bleeding. The arterial blood pressure was 50/0 mmHg, HR 135 beats per min, and peripheral pulse non-palpable. The skin and conjunctivas were pale. The patient was able to breath independently with the passive oxygen supplementation (6 liters per min); the oxygen saturation determined without the oxygen support amounted to 87%. Heavy uterine bleeding was documented on pelvic examination. The endocervical canal was dilated by a hematoma to about 5 cm in diameter. An extensive fluid resuscitation with colloids and crystalloids was implemented. Before the group-matched blood B Rh(+) was available, 2 units of universal Rh(-) blood were transfused. The patient was transferred to a surgical block on an emergency basis and subjected to laparotomy under general endotracheal anesthesia. The status of the patient was unstable despite extensive anesthetic and surgical management, and an infusion of noradrenaline (0.5 µg/kg/min) was required. Moreover, a recombinant factor VIIa (8 mg) was administered intravenously due to persistent severe hemorrhage, with resultant marked reduction of bleeding. Bilateral uterine arteries were closed through the Kelvin-Chrobak vaginal access. Overall, 6 units of erythrocyte concentrate, 8 units of FFP, 6 units of CPAG, and 6 units of platelet concentrate were transfused intraoperatively, along with 1500 ml of crystalloids and 1250 ml of colloids. The abdominal cavity was closed with leaving two thick latex Redon drains, and the Kehr's drain was inserted into the vagina. The patient was transferred to the Intensive Care Unit where the synchronized intermittent mandatory ventilation was continued for two days. Hematological consultation was ordered due to perioperative hemostatic disorders, and von Willebrand factor antigen (vWF:Ag 83.25% norm: 60-200%), and the activities of factor VIII (182.96%, norm: 70-150%) and factor IX (84.42%, norm: 70-120%) were determined aside from the other laboratory parameters (Tables 1-3). The patient, with normalized cardiovascular and respiratory function, was transferred to the Department of Obstetrics on postoperative day 3, and discharged home on the day 7.

However, two days following the discharge the patient was readmitted to the clinic due to vaginal spotting. Her blood pressure and HR amounted to 130/80 mmHg and 68 beats per min, respectively, but she required continuous infusion of blood preparations due to persistent bleeding. Her general status improved upon administration of recombinant factor VIIa and continuous infusion of erythrocyte concentrate, FFP, and CPAG. The concentration of hemoglobin ranged between 4.8 and 7.2 mmol/L (norm: 12.0-16.0 mmol/L) depending on the amount of transfused blood. Control abdominal ultrasound revealed the anteroflexion of physiologically-shaped uterus, and homoechogenic myometrial structure without focal lesions. The uterine cavity was empty but a 5 x 2 cm mass, corresponding to clotted blood, was documented in the uterorectal pouch. Due to severe vaginal bleeding observed on the second day of hospitalization, subsequent deterioration of patient's status and the signs of hypovolemic shock, she was qualified to another laparotomy. A single 8.0 mg dose of recombinant factor VIIa was administered intravenously prior to the transfer to surgical block. Adhesions between the omentum and the anterior abdominal wall were revealed during the laparotomy, along with numerous necrotic, partially decaying lesions at the cesarean section scar, and infiltration of the round and the infundibulo-pelvic ligaments. Due to persistent bleeding and associated hemostatic disorders, the patient was qualified to selective hysterectomy. Recombinant factor VIIa (2.0 mg) was administered preoperatively in a fast intravenous infusion, with resultant normalization of hemostasis. The uterus was removed at the level of the vaginal fornix. The patient was transfused 3 units of erythrocyte concentrate , 6 units of FFP, and 6 units CPAG intraoperatively. Abdominal wall was closed with leaving two thick latex Redon drains and the Kehr's drain. The results of perioperative laboratory parameters are presented in Tables 4 and 5. Control functional tests of the thyroid suggested subclinical Hashimoto hypothyroidism: TSH 11.72 µIU/ml (norm: 0.270-4.20 µIU/ml), FT3 1.98 pg/ml (norm: 2.00-4.40 pg/ml), FT4 1.12 ng/dl (norm: 0.930-1.70 ng/dl). Consequently, the dose of L-thyroxin was escalated from 50 µg to 75 µg per day. After 11 days of treatment, the patient was discharged home in good general status and with normalized complete blood count and coagulation profile. A hematological consultation was recommended as the presence of potential bleeding disorder could not be excluded during hospitalization due to the necessity of FFP, CPAG, and recombinant factor VIIa transfusion. The determination of coagulation profile and vWF was ordered at least 14 days after the last transfusion.

The results of the control tests conducted at the Department of Hematology were as follows: activity of vWF (the activity of ristotecin cofactor, vWF:Ac) 16% (norm: 50-150%), vWF:Ag 29%, concentration of factor VIII 48% (Table 6). A suspicion of von Willebrand disease/syndrome was raised on the basis of clinical presentation and the results of the tests. The patient was administered vWF (3 x 500 units) at two-day intervals, along with two doses of factor VIII (1000 units), and recombinant factor VIIa (7 doses, each 40 µg/kg, during two days). The level of TSH was re-evaluated due to still low values of vWF:Ac and vWF:Ag. As it amounted to 18.98 µIU/ml, the dose of L-thyroxin was further escalated to 100 µg per day, and another two doses of vWF (500 units each) were administered along with recombinant factor VIIa (80 µg/kg). The patient was referred to the Institute of Hematology with the preliminary diagnosis of type 1 vWF deficiency.

Discussion

Acquired von Willebrand syndrome (AvWS) is a rare form of bleeding disorder with similar clinical manifestation as inherited vWD. AvWS may be associated with a number of other conditions; it is diagnosed in individuals with neither personal nor family history of bleeding disorders.

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The literature evidence of this condition is sparse. Similar to inherited vWD, typical signs of AvWS include epistaxis, predisposition to bruising, prolonged bleeding after cuts, dental procedures or surgeries, and heavy, prolonged periods that often lead to anemia. Rarer signs of the condition include postoperative and postpartum hemorrhage, and intra-articular bleeding. In most patients with AvWS, both the synthesis and release of vWF to circulation are normal. Principal laboratory findings that support the diagnosis of AvWS include decreased activity and (rarer) concentration of vWF. AvWS may be associated with such conditions as hypothyroidism, autoimmune disorders, malignant lymphoma, myeloproliferative disorders, infectious diseases, solid tumors, metabolic disorders, liver cirrhosis and congenital valve defects [5-7]. Decreased activity of vWF develops in an autoimmune mechanism, namely due to presence of specific and non-specific autoantibodies that form immune complexes with vWF, and as a result of enhanced enzymatic proteolysis of this factor [5,6]. Hypothyroidism is associated with both decreased activity and lowered concentration of vWF, which is explained by inhibited synthesis of protein resulting from thyroxin deficiency [5-10]. Moreover, AvWS may result from the intraoperative infusion of synthetic colloids, and especially hydroxyethylated starch of older generation, whose administration is known to cause the depletion of high-molecular-weight vWF multimers.

The diagnosis of either type 1 vWD or AvWS may be challenging. Both vWF and factor VIII are acute phase proteins, and thus their concentrations may increase in response to stress or physical exercise, during menstruation, inflammation and infection, after surgeries and transfusions of plasma products (FFP, cryoprecipitate). Physiological concentrations of vWF and factor VIII are person-specific and usually increase with age, which necessitates their repeated measurements in some cases. Patients with vWD typically present with normal prothrombin and thrombin times and normal concentration of fibrinogen. aPTT may be prolonged in individuals with decreased activity of factor VIII, including some persons with type 1 vWD. However, most patients with vWD present with normal coagulation profiles.

The hereby presented patient was eventually diagnosed with autoimmune hypothyroidism and vWF deficiency. The heavy vaginal bleeding observed perioperatively might be associated with the depletion of vWF due to thyroxin deficiency. Moreover, the level of high-molecular-weight vWF multimers might be additionally decreased due to the intraoperative infusion of hydroxyethylated starch. The substitution of FFP and cryoprecipitate was reflected by a transient increase in the concentrations of factor VIII and vWF (half-lives of ca. 12 h and 10-26 h, respectively), which markedly hindered perioperative diagnosis.

However, further comprehensive analysis of familial history and the examination of family members revealed the deficiency of vWF in the patient's brother as well. In contrast to his sister, however, he showed predisposition to epistaxis and bruising. It is not surprising, as clinical manifestation of inherited vWF deficiency can differ considerably among family members despite the presence of similar defect documented on laboratory testing. The genotypic and phenotypic variability is particularly often in type 1 of the condition, i.e. that suspected in our patient. Also the group of blood can modify the course of the disease: the average plasma activity of vWF in individuals with group O is 25-35% lower than in those with the other groups [11]. This may explain differences in the phenotypic manifestation of vWF deficiency in our patient and her brother, having groups B and O, respectively.

Only a few previous studies analyzed the incidence and severity of bleeding associated with vWD [12-14]. The results of these studies suggest unequivocally that it is type 3 vWD which is associated with most severe bleeding disorders.

The diagnostics of vWD should comprise screening tests, followed by further detailed examination to confirm or exclude the condition. The screening tests used in the detection of vWD include determination of platelet count (usually normal in type 1 vWD), bleeding time (prolonged in most cases, but normal in mild forms of vWD), prothrombin time (usually normal) and APTT (prolonged proportionally do the degree of factor VIII deficiency). Confirmation of vWD and identification of its type require functional testing, e.g. ristotecin cofactor activity assay (vWF:RCo). This is the basic screening test of vWF activity, examining interaction of this factor with thrombocyte receptors. Another useful test is determination of vWF concentration with an aid of polyclonal antibodies, i.e. the measurement of vWF antigen (vWF:Ag). The levels of vWF antigen are decreased in type 1 vWD, undetectable in type 3, and normal in type 2 of the condition. Another important diagnostic parameter is the activity of factor VIII (FVIII) (Factor VIII coagulant portion, FVIII:C). FVIII:C is very low in type 3 vWD, and moderately decreased in types 1 and 2. Equally important is the qualitative analysis of vWF multimeric structure on agarose gel electrophoresis; normal structure of the multimers is observed solely in type 1 and 2 vWD. The type of vWD can be also identified on the basis of ristotecin-induced platelet aggregation (RIPA); enhanced binding of vWF to thrombocyte receptors is specific for type 2 vWD. Also determination of vWF content in thrombocyte granules can be helpful in the diagnostics of vWD, as this parameter indirectly reflects the level of vWF in endothelial cells. The platelet vWF test allows to distinguish between the three subtypes of type 1 vWD: 1) with normal vWF content (platelet-normal), 2) with low vWF content and normal function thereof (platelet-low), and 3) with normal content but impaired function of vWF (platelet-discordant). The laboratory parameters of our patient corresponded to type 1, subtype 1 vWD. Initial diagnostics of AvWS is similar as in the case of vWD, and these two conditions cannot be distinguished on the basis of the coagulation profile. Important diagnostic criteria of AvWS include lack of family history of bleeding disorders and older age at the onset of symptoms. The list of laboratory tests that can be helpful in distinguishing between AvWS and vWD includes vWF-to-collagen binding assay and the abovementioned agarose gel electrophoresis. It is of note that pregnancy, stress, and inflammation markedly modulate the plasma activity of vWF [15]. Adaptation of the clotting system to growing pregnancy results in impairment of fibrinolysis and overactivation of factors involved in clot formation. An increase in the synthesis and concentration of most plasma clotting factors (except from factor XIII) is accompanied by placental overexpression of the tissue factor (TF). Although during the 1st and 2nd trimester, the increase in the synthesis and concentration of factor VIII in patients with type 1 vWD is less evident than in normal pregnant women, these parameters normalize at birth. Both the concentration and activity of vWF increase

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systematically as early as about the 6th week of gestation, and during the third trimester are usually 2- to 5-fold higher than respective preconception levels; this can hinder the diagnosis of vWF deficiency. However, it should be remembered that the levels of vWF decrease dramatically shortly after delivery (especially during the first 24 h) and within few/several days normalize at their preconception levels; this can be reflected by persistent postpartum hemorrhage. This decrease can be delayed due to regular breastfeeding. Moreover, patients with vWD significantly more often than normal women present with late postpartum hemorrhage (3 to 5 days post-partum), as observed in the hereby presented case.

vWD can be treated with desmopressin, stimulating the release of vWF from vascular endothelium, or with a substitution therapy with plasma-derived products containing vWF. Implementation of either the treatment results in normalization of impaired adhesion and aggregation of platelets and reversal of the vWF-dependent defect of intrinsic coagulation pathway, resulting from factor VIII deficiency. Adjunct treatments include administration of anti-fibrinolytic amino acids (aminohexanoic acid [EACA], tranexamic acid [Exacyl] and estrogens [16].

Intravenous administration of FFP, cryoprecipitate (containing factor VIII, vWF, fibrinogen and fibronectin) and recombinant factor VIIa caused transient normalization of factor VIII/vWF in our patient (Table 1). Nevertheless, the secretion of endogenous vWF was still impaired (Table 6), which was reflected by another episodes of vaginal bleeding. The bleeding might result from poor quality of the vWF-containing preparations administered to our patient, namely from the loss of biological activity of the factor during processing of plasma. Furthermore, low activity of the preparations used in the hereby reported case might reflect the activity of platelet and leukocyte proteases present in the fractioned plasma. Therefore, it should be remembered that even the best preparations of VIII/vWF cannot counterbalance the defects of endothelial cells or platelets in patients with vWD.

The aim of this case report is to emphasize the risk for AvWS which is inherent to various conditions, including hypothyroidism. Administration of rVIIa should be considered in individuals who do not respond adequately to routine treatments. Administration of rVIIa likely improved hemostasis of our patient, especially its hypothyroidism-related component, which is of vital importance in the case of DDAVP-resistant disease. Identification of underlying condition and prompt implementation of its treatment is crucial in all individuals with suspected vWD. Although we used this approach in our patient, neither the concentration nor the activity of vWF increased despite normalization of the thyroid function. It should be remembered that the inherited form of vWD (likely presented by our patient in view of her brother's medical history) necessitates appropriate preoperative treatment. It was the co-existence of several important risk factors, i.e. hypothyroidism, stress and pregnancy which triggered clinical manifestation of previously asymptomatic inherited vWD in our patient. Despite causative treatment, i.e. normalization of thyroid function, we did not manage to control vWD in the hereby reported case, and thus the patient was referred for further specialist evaluation and treatment at the tertiary center.

Table 1. Activity of clotting factors

Parameter	Value	Units
von Willebrand factor antigen (vWF:Ag)	83.25 (normal limits: 52-154 for group 0 blood, 60-200 for the remaining blood groups)	%
Activity of factor VIII (VIIIF)	182.96 (normal limit: 70-150)	%
Activity of factor IX (IXF)	84.42 (normal limit: 70-120)	%

Table 2. Complete blood count prior to and after rFVIIa administration

Parameter	WBC (G/L)	RBC (T/L)	HBG (g/dL)	HT (%)	PLT (G/L)
Normal limit	4.00-10.0	3.50-5.20	12.0-16.0	36.0-50.0	140.0-440.0
Before surgery	6.37	2.69	5.54	16.15	375.0
2 h post-rFVIIa	19.8	3.69	5.75	20.1	327.0
12 h post-rFVIIa	17.9	4.15	11.65	34.55	197.0

Table 3. Coagulation profile prior to and after rFVIIa administration

Parameter	AT III (%)	APTT (s)	PT (s)	INR	Fibrinogen (ng/dl)	D-dimers (µg/l)
Normal limit		24.8-37.2	11.0-16.5	0.8-1.2	158-540	1-500
Before surgery	87.5	29.9	13.9	1.07	541	524
2 h post-rFVIIa	80.2	39.9	14.5	1.09	364	396
12 h post-rFVIIa	207	27.8	13.6	1.09	384	380

Table 4. Complete blood count prior to and after rFVIIa administration during hysterectomy

Parameter	WBC (G/L)	RBC (T/L)	HBG (g/dL)	HT (%)	PLT (G/L)
Normal limit	4.00-10.0	3.50-5.20	12.0-16.0	36.0-50.0	140.0-440.0
Before surgery	12.6	2.57	7.41	21.9	363.0
2 h post-rFVIIa	15.8	2.65	7.23	20.1	297.0
12 h post-rFVIIa	13.9	5.17	11.65	33.5	250.0

Table 5. Coagulation profile prior to and after rFVIIa administration during hysterectomy

Parameter	AT III (%)	APTT (s)	PT (s)	INR	Fibrinogen (ng/dl)	D-dimers (µg/l)
Normal limit		24.8-37.2	11.0-16.5	0.8-1.2	158-540	1-500
Before surgery	87.5	32.6	12.9	0.87	757	486
2 h post-rFVIIa	80.2	30.9	10.5	0.76	657	1261
12 h post-rFVIIa	207	32.8	10.8	1.00	660	370

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Table 6. Laboratory parameters of the patients determined at the Department of Hematology

Parameter	Value
Ristotecin cofactor activity (AWF:RCo)	16% (normal limit: 50-150%)
von Willebrand factor antigen (vWF:Ag)	29% (normal limit: 50-200%)
Activity of factor VIII (FVIII:C)	48% (normal limit: 50-200%)
Ristotecin-inducted platelet aggregation (RIPA)	>5 at 4 min (norm: >5 at 4 min)

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