Bernard-Soulier Syndrome In Pregnancy: A Case Report

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Citation

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Abstract

Bernard-Soulier syndrome (BSS) is a rare inherited disorder with giant platelets, thrombocytopenia and a prolonged bleeding time. These abnormalities are caused by genetic defects of the glycoprotein (GP) Ib/IX/V complex that constitutes the von Willebrand factor receptor on the platelet surface. We present the case of a 19-year-old pregnant woman with Bernard-Soulier Syndrome. A cesarean operation under general anesthesia was carried out at 38 weeks of pregnancy. No complications were seen in the ante-natal period, the delivery and post-partum course. The platelet concentrations were given ante-natally and after delivery. Women with BSS should be observed at an appropriate centre using a multidisciplinary approach. The primary treatment remains platelet transfusion. Appropriate individualised therapy for BSS should be defined and new studies are needed on the role of the glucoprotein Ib-IX-V complex in regulating platelet turnover to better depict the clinical course.

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INTRODUCTION

Bernard-Soulier syndrome (BSS) is a rare inherited bleeding disorder characterized by a prolonged bleeding time, moderate thrombocytopenia, giant platelets on a peripheral blood smear and defective platelet agglutination to ristocetin. BSS results from the dysfunction or absence of the receptor for von Willebrand factor (vWF) on the platelet surface, platelet glycoprotein (GP) Ib/IX/V complex, that mediates platelet agglutination in response to ristocetin and platelet adhesion to damaged vascular wall [1,2]. The response to collagen is blunted. BSS is caused by genetic defects in the genes of GPIb, GPIb, GPIX or GPV [1,2]. This variety of mutations could explain the heterogeneity of this syndrome. Four different features of BSS may contribute to the hemorrhagic diathesis: thrombocytopenia, abnormal platelet interaction with vWF, abnormal platelet interaction with thrombin, and abnormal platelet coagulant activity [2].

Because of its rarity, there exist only a few and divergent reports on the value of obstetric management of this disorder. Therefore, our aim was to evaluate a pregnant woman with Bernard-Soulier Syndrome with regard to the obstetric and anesthetic management, and complications influencing clinical outcome.

CASE REPORT

A 19-year-old primigravid woman was sent to the state hospital for routine care of pregnancy where thrombocytopenia (78.000/µL) was found incidentally and therefore she was referred to the department of hemathology at 34 weeks' gestation. At this time, the diagnosis of BSS was made on the basis of a prolonged bleeding time (5 min), thrombocytopenia (80-90.000/µL) with giant platelets and absence of ristocetin-induced platelet agglutination. She had had no history of spontaneous nasal or mucosal bleeding in childhood but her mother had the history of bleeding diathesis. The patient was hospitalized at 38 weeks of pregnancy in our Department with irregular contraction. On physical examination, patient was obese and her vital parameters were stable. Systemic examination was within normal limits. No abnormalities were seen on ultrasound examination and fetal growth corresponded with gestational age. Prenatally, she was transfused with four units of platelets to maintain the platelet counts above 50.000. However, although an induction of the labor had been started, because of the labor arrest and fetal distress, and the potential risk of neonatal thrombocytopenia, a cesarean operation was done under general anesthesia and delivery of a 2540 g female fetus was achieved. The Apgar scores were 1 and 5 at 6 and 8 min, respectively. The procedure was uncomplicated, and estimated blood loss was 1600 mL. Her postoperative platelet count was 76.000/µL. The newborn's hematocrit was 42% and platelet 307.000/µL. A specific gene analysis to rule out BSS in the neonate could not be

performed. The remaining postoperative course was uneventful. Initially, we aimed to not transfuse the patient with platelets postoperatively because of alloimmunization to platelets, however since the platelet count had decreased to 7500/μL and the hemoglobin to 9.2 g/dL, she received 2 units of red blood cells and two units of platelets and dexamethasone, administrated intravenously at a dose of 10 mg every 12 hours and of 5 mg every 12 hours was given after delivery. She was discharged on postoperative day 8 with platelet count 44.000/μL; coagulation studies were normal.

DISCUSSION

BSS is normally inherited in an autosomal recessive way and when homozygous is often due to consanguinity, only one case was described as autosomal dominant [3]. More than 30 mutations of the GPIb, GPIb, or GPIX genes have been described in BSS. Recent studies also have shown that the phenotypes caused by mutations in the subunits of the GPIb/IX/V span a wide spectrum, from the normal phenotype, to isolated giant platelet disorders/macrothrombocytopenia, to full-blown BSS and platelet-type von Willebrand disease. Although recent progress in molecular biology has clarified the genotype-phenotype relationships of the GPIb/IX/V disorders, a close examination of platelet morphology on blood smears is still indispensable for a proper diagnosis. In addition, Gruel Y et al. [4] suggested that immunological techniques can be applied as early as 18 weeks of gestation for the antenatal diagnosis of BSS by direct puncture of the umbilical vein.

Typical symptoms include epistaxis, easy bruising, prolonged bleeding with superficial injuries, abnormal menstrual periods, bleeding gums and hemorrhage associated with trauma, intraoperative and postoperative bleeding. As was seen in this present case, in some patients the disease can go unrecognized until the third or fourth decade [5]. In some patients the pregnancy course was smooth while in others severe bleeding at the time of delivery and delayed postpartum hemorrhage were prominent features [6]. In the present case, no complications had been seen in the ante-natal period, the delivery and post-partum course. Although the patient's mother had a history of bleeding diathesis and although thrombocytopenia may develop or become aggravated in patients with BSS, it is unclear whether thrombocytopenia exacerbates bleeding during pregnancy. Further complicating this woman's pregnancies was the development of antibodies to platelet glycoprotein IB/IX, leading to fetal thrombocytopenia and massive intracranial bleeding, and neonatal alloimmune thrombocytopenia [7].

CBC that may reveal normal or occasionally low, platelet counts may range from <30.000/μL to marginally low or normal, prolonged skin bleeding time, normal PT, PTT. BSS platelets differ from normal platelets also in size and membrane composition [1,2]. Platelet aggregation studies show normal response to ADP, epinephrine, collagen and arachidonic acid with no response to ristocetin. BSS platelets also have a reduced response to low doses of thrombin [8] and abnormal procoagulant responses [9]. They have both an increased resting procoagulant state and do not show a normal increase in procoagulant activity after stimulation. Laboratory studies can detect the defective gene responsible for these platelet disorders. Genetic counseling may be of value to couples with a family history of any of these disorders who are planning children in the future.

Because of the risk of severe neonatal thrombocytopenia remains uncertain, the mode of delivery of BSS patients remains controversial and is similar to that for ITP. Because of the theoric risks of intracranial hemorrhage to thrombocytopenic fetuses, although many authors have advocated cesarean section for women with ITP [10] and although some authors found that the severity of thrombocytopenia in the newborn correlated closely with the severity of maternal disease [10] there is a trend towards the decision on vaginal route delivery in the recent literature because of the risk of maternal bleeding at surgery. However, it is difficult to predict during antepartum period which baby will be thrombocytopenic. Therefore we aimed to use fetal scalp blood sampling for platelet determinations to determine the safety of vaginal delivery. However, because of the limited cervical dilation and a high presenting part, this tecnique could not be performed. It has been also reported that if blood clots are present in the sample, a falsely low platelet count can occur. Alternatively, percutaneous umbilical cord sampling (PUBS) has been proposed to determine the potential severity of the neonatal thrombocytopenia [10]. However, due to the rarity of this disorder, limited number of cases in published studies, the thrue risk of PUBS in BSS is not well established. On the other hand, this treatment requires expertise available in a tertiary care setting and is not universally accepted because of the potential risks involved with repeated cordocenteses especially in early trimester of pregnancy such as cord hematomas or other mishaps [11]. In addition, intracranial hemorrhage has also occurred as early as the end of the first

trimester when intrauterine platelet transfusion is not yet possible [12]. Therefore, PUBS is generally not recommended until pulmonary maturity is present in the event that complication from the sampling procedure necessitates emergency cesarean section. On the basis of the previous reported data, we concluded that cesarean section is not routinely indicated as the method of delivery for parturient patients with BSS and the vaginal route may be considered unless otherwise obstetrically indicated. However, in addition to the labor arrest, fetal scalp blood sampling or PUBS could not be performed in the present case, therefore, she underwent cesarean section and gave birth normally to a healthy child.

The anesthetic implications of this syndrome are not well known because few cases have been reported in the literature. Some author advocate that epidural or spinal anaesthesia should be avoided in patients with platelet counts less than 50.000 /µl, because of the risk of epidural hemorrhage due to thrombopenia [13]. Although there is data indicating that regional anesthesia may be safely administrated in women when the platelet count is <100.000/µl without prolonged PT/PTT [14], in the present study, anesthesia was induced with fentanyl and diazepam, and was maintained with nitrous oxide, fentanyl, and 0.5% enflurane. The use of halothane should be avoided in patients with BBS because it may inhibit the aggregation of platelets and prolong the bleeding time.

There is no specific treatment for BSS. Most patients, by taking adequate precautions by avoiding minor trauma and use of antiplatelet medications, live relatively normal lives. At menarche, oral contraceptives are often necessary to control menorrhagia. Platelet transfusion is the mainstay of therapy for serious bleeding in patients with BSS, and is given prophylactically before surgical procedures. Precautions to avoid catastrophic bleeding should be taken. In the present case, preoperative prophylactic platelet transfusion was carried out with no adverse events. The other treatment procedures are immune suppression with steroids and intravenous gamma globulin plasmapheresis [15] and hematopoietic stem-cell transplantation from HLA-identical siblings [16] in patients with severe, repeated, life-threatening hemorrhages who develop anti-glycoprotein lb/IX/V alloantibody with subsequent refractoriness to platelet transfusion. 1-deamino-8-D-arginine vasopressin (DDAVP) may shorten the bleeding time in some [17] but not all [18] BSS patients. The use of antifibrinolytic drugs, such as e-aminocaproic acid or tranexamic acid, may or may not be beneficial [7,18]. In some cases, splenectomy has apparently been beneficial although the high risk for perisurgical hemorrhage [17]. On the other hand, Magann et al. [13] proposed a therapeutic protocol based on the administration of high doses of dexamethasone aimed at inducing fetal lung maturity, promoting a significant improvement of the clinical parameters of arterial pressure and the laboratory parameters of platelet count, LDH and AST associated with HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Although there is insufficient evidence to determine whether adjunctive steroid use exerts a benefical effect to increase platelet counts or to prevent significantly antiplatelet alloantibodies in the BSS, this current study demonstrated that corticosteroid produced a little improvement in the platelet count. Also, it seems reasonable to consider that the use of high dose glucocorticoid therapy preoperatively could potentially have benefit to provide to use regional anesthesia by increasing the maternal platelet count. Thus, maternal morbidity risk associated general anesthesia including failed intubation, aspiration and neonatal depression is superior when compared to regional anesthesia [11]. But, the dose, duration of therapy, and choice of steroid that can optimize the outcome for women with BSS requires further investigation.

CONCLUSIONS

In conclusion, women with BSS should be observed at an appropriate centre using a multidisciplinary approach. The primary treatment remains platelet transfusion. Appropriate individualised therapy for BSS should be defined and new studies are needed on the role of the glucoprotein Ib-IX-V complex in regulating platelet turnover to better depict the clinical course.

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