Management of pregnancy in a patient with severe haemophilia A

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Haemophilia A is a bleeding disorder that has a spectrum of manifestations ranging from persistent bleeding after minor trauma to spontaneous haemorrhage. As an X-linked disease, it has a rare occurrence in females. We report a case of a pregnant patient with severe haemophilia A, who received epidural analgesia during labour. The prepartum, intrapartum and postpartum care of a patient with such a bleeding diathesis is discussed.

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Pregnancy is normally associated with changes in the coagulation system. These include accelerated platelet activation and increased platelet turnover, as well as an increase in the plasma concentration of clotting factors, including factors I (fibrinogen), V, VII, VIII, IX, X and XII. As an example, factor VIII levels normally increase by 200–500% late in pregnancy.¹ There is also enhanced fibrinolysis with increased thrombin production. This state of accelerated but compensated intravascular coagulation serves as a protective mechanism to curb maternal blood loss during delivery.

On occasion, labour analgesia in the form of neuraxial block is provided to patients with haematological disorders. Coagulation factor deficiencies and thrombocytopenia can increase both anaesthetic and obstetric risks. Performing neuraxial block in patients with these disorders risks the development of an epidural haematoma, a potentially catastrophic complication that can lead to permanent paralysis.

A well-known coagulation factor disorder is classical haemophilia A, an inherited condition characterized by potentially severe mucocutaneous and deep tissue (joint and muscle) bleeding, which results from a deficiency in clotting factor VIII. Haemophilia A occurs with an incidence of 1 in 5000 male births.² The gene for factor VIII is located on the long arm of the X chromosome. Therefore, haemophilia has a classic sex-linked mode of transmission. Female offspring born to haemophilia carriers will have a 50% chance of being a carrier of the disease. Furthermore, it is estimated that 1 in 100 000 women is a symptomatic haemophilia A carrier (factor VIII levels ≤0.3 U ml⁻¹) and at risk of mild or moderate bleeding symptoms. However, severe haemophilia A (factor VIII <0.01 U ml⁻¹), a condition that places a woman at risk for severe bleeding complications, is an extremely rare event.

A deficiency in factor VIII is suggested by a significant prolongation of the activated partial thromboplastin time (APTT) and confirmed by a factor VIII activity assay.
Haemophilia severity is classified according to the baseline level of clotting factor activity. Factor VIII activity levels are reported in units, with 1 U ml⁻¹ corresponding to 100% of the factor found in 1 ml of normal plasma. Normal plasma activity levels usually range between 0.5 U ml⁻¹ and 1.5 U ml⁻¹ (50–150%).³ Severely affected patients have <1% of normal factor levels, while those with moderate disease have 1–4%, and patients with mild disease have 5–50%. ⁴ Those with <1% of normal factor VIII level are susceptible to spontaneous bleeding episodes such as haemarthrosis, soft tissue haematoma, and intracranial haemorrhage. All patients with haemophilia, regardless of the severity of the disease, are at risk of excessive bleeding during surgery.

We report a case of a 30 yr-old female with severe haemophilia A (factor VIII level <1%) who delivered her first baby at term under epidural analgesia.

Case report

The patient is a 30-yr-old female primigravida with severe haemophilia A who presented in labour at the 39th week of pregnancy. The patient was diagnosed with haemophilia A in early childhood, subsequent to the development of mucocutaneous and deep tissue bleeding. Her haemophilia mutation has not been identified, but her disease was determined to be the result of skewed non-random X-inactivation.⁵ A mutation has not been identified in any of her first degree relatives nor did they have any clinical evidence of the disease. Her bleeding history has been mild, targeting mainly her ankle joints. She has had minimal intra-articular bleeding in her adult life. There was no history of menorrhagia. The young woman had been receiving lifelong care through the comprehensive haemophilia treatment centre at our institution.

The coordination of medical and obstetrical prenatal care for this patient was carefully planned before her pregnancy. Pregnancy was uncomplicated by haemorrhage, as she was maintained on 30 U kg⁻¹ of i.v. recombinant factor VIII concentrate (Helixate FS-grow, Aventis Behring) once or twice weekly as part of a self-administered home infusion programme. Amniocentesis was performed without bleeding after correction of the patient’s factor VIII level to 100% of normal. The patient was determined to be carrying a female fetus that had received the mother’s inactivated and presumed unaffected X chromosome and was, therefore, expected to be unaffected by haemophilia A. This was important to ascertain so that delivery could be planned to be as atraumatic as possible.

The patient presented in labour after she experienced spontaneous rupture of her membranes. Her physical examination was unremarkable, with no evidence of ecchymoses, petechiae or purpura. The patient prophylactically self-administered factor VIII infusion before presenting to the hospital. Laboratory results were obtained within 30 min of the self-administered 50 U kg⁻¹ factor VIII infusion that raised plasma factor VIII levels to 1.0 U ml⁻¹ (100% of normal levels). Her white blood cell count was 15 000 ul⁻¹ haematocrit 36.3%, platelet count 224 000 mm⁻³, prothrombin time (PT) 12.0 s, and APTT 33.4 s. As expected from the pre-labour discussions between the anaesthetist and the patient, she requested placement of epidural analgesia in labour.

Before the placement of an epidural catheter, the patient’s haematological status had to be optimized. Two large bore i.v. lines were placed. Management of her Factor VIII deficiency was performed in conjunction with her haematologist. The plan was to normalize the patient’s plasma factor VIII level for delivery using a continuous infusion of Helixate FS® at a rate of 3 U kg⁻¹ h⁻¹ through a dedicated line. Fifteen minutes after the infusion was started, a blood sample was sent for determination of PT, APTT, fibrinogen levels, and factor VIII levels. Regional anaesthesia was only to be performed after the results of these variables were known to be haemostatic. Otherwise, i.v. narcotics were to be used for analgesia in labour. After infusion of the recombinant factor VIII, the laboratory data revealed the following: PT 12.5 s, APTT 33.3 s, fibrinogen level 533 mg dl⁻¹, and factor VIII level 1.01 U ml⁻¹ (101% of normal).

An epidural was placed using a 17-gauge Hustead needle at the L3–4 interspace using the midline technique, on the first attempt. There was no evidence of bleeding during needle placement. The patient was given an initial dose of bupivacaine 0.25%, 10 ml upon initiation of epidural analgesia. The patient delivered by spontaneous vaginal delivery without any excessive vaginal bleeding, approximately 3 h after epidural placement, and required only one 10 ml dose of lidocaine 1.0% for the second stage of delivery. Her post-partum course was also uncomplicated. She was maintained on a Helixate FS® infusion at a rate of 3 U kg⁻¹ h⁻¹ for 48 h (factor VIII levels, 0.78–1.11 U ml⁻¹) without any excessive post-partum bleeding or symptoms of epidural haematoma. Mother and daughter were discharged after three days and maternal haemostasis prophylaxis was continued for six weeks postpartum. The lowest acceptable haemostatic factor VIII levels were targeted at 0.5 U ml⁻¹ (days 3 and 4); 0.3 U ml⁻¹ (days 5–7); 0.1 U ml⁻¹ (days 8–14); and 0.05 U ml⁻¹ (week 3 until cessation of post-partum bleeding at week 6). She experienced minimal post-partum bleeding. At that time, the patient was also determined to be negative for the development of an acquired inhibitory antibody to factor VIII.

Discussion

The gene encoding factor VIII is located on the long arm (q) of the X chromosome, specifically in band Xq28. Normally, one of the X chromosomes in females is randomly inactivated in a process described by Lyon and subsequently known as lyonization. This inactive X chromosome is known as the Barr body.⁶ In a hetero-
zygous female, approximately equal portions of normal and defective X chromosomes are inactivated in somatic cells. In this patient, the normal X chromosome was non-randomly inactivated which allowed the defective gene on the active X chromosome to become manifest. This skewed inactivation or extreme lyonization of the normal X chromosome in a heterozygous female has been described previously.7,8

Many types of chromosomal irregularities can result in the same disease. Structural gene defects such as mutations, deletions, inversions and translocations may cause the condition to become manifest. For example, a patient may be truly homozygous resulting from a haemophilic father and a carrier mother.9 In addition, an abnormal gene may result from a spontaneous mutation,10 or result from a chance mutation of the paternal X chromosome at conception,11 with subsequent inactivation of the normal X chromosome causing the disease to become manifest. A case of both maternal and paternal de novo germline mutations also resulted in haemophilia.12

Furthermore, certain karyotype defects may also express a mutation of a defective gene. A phenotypically normal female, with 46, XY/45, XO mosaicism, who was the offspring of a maternal carrier and an unaffected father, was noted to have the disease.13 Phenotypic females with testicular feminization (46, XY) may also have the disease.14 Another patient was described to have inherited a defective maternal X, and a paternal isochromosome (Xq), which is a chromosome containing two copies of the long arm. The haemophilic trait on the structurally normal but defective maternal X chromosome was fully expressed.15 Similarly, in another case, a patient with Turner’s syndrome (45, XO) inherited only a defective maternal X chromosome without the paternal X chromosome.16

The treatment of haemophilia has progressed in recent years. Transfusion therapy was first used in the 1840s to manage postoperative bleeding.3 However, it was not until 100 yr later, when clotting factors were discovered and the deficiencies in haemophiliacs identified, that transfusion therapy with fresh frozen plasma was used routinely.3 Cryoprecipitate was discovered in the 1960s, and early factor VIII concentrates were first used in an effort to significantly improve the patient’s quality of life in the early 1970s.2 Since these blood products were made from numerous pooled blood donor collections, up to 90% of patients with haemophilia suffered from transfusion-transmitted viral infections, such as HIV-1 and hepatitis B and C.3 Mandatory screening of all donor plasma for these and other infectious agents as well as the viral attenuation of all such products were universally instituted in the 1980s, and improved in the 1990s.17 Since then, there has been no transmission of these viruses from blood products. Ultimately, the cloning of the genes for both factor VIII and IX allowed the development of recombinant clotting factor concentrates that have further reduced the now theoretical risk of therapy-transmitted infection.18

Fortunately, because this patient was not actively infected with either HIV or the hepatitis viruses, there was no fetal risk of perinatal viral transmission. Furthermore, the availability of safe and effective recombinant factor VIII concentrates allowed haemostasis prophylaxis without any infectious risk to the fetus/newborn. Prophylaxis during the antepartum period was maintained because there is an increased chance of fetal loss, particularly in the first trimester, in patients with coagulopathies.19,20 As the patient’s factor VIII level had been increased into the normal haemostatic range, an estimated blood loss of 500 ml for a routine vaginal delivery was expected. However, complications leading to excessive blood loss may occur in any patient, including vaginal tears, cervical tears, retained placenta, or uterine atony. Surgical intervention may be necessary and Caesarean delivery may be required for arrested labour or fetal distress. Preparations for managing excess blood loss included ensuring that the patient had two large bore i.v. lines and that blood was immediately available for transfusion.

The patient presented in this case report had a known rare congenital bleeding disorder, but a parturient with a bleeding diathesis may occasionally present to a labour and delivery suite without warning. This may result from an acquired or inherited coagulation disorder such as thrombocytopenia, von Willebrand disease (type 2 and 3), coagulation factor deficiency, or from an iatrogenic cause, as is the case with the use of anticoagulant medication. These patients can present a unique challenge to the anaesthetist. If the decision is made to proceed with neuraxial anaesthesia, a subarachnoid block using a small gauge spinal needle may be preferable to epidural anaesthesia.21 This is not always practical, especially for women in labour who will require repeated doses of local anaesthetics. The epidural catheter should be placed in the midline and analgesia produced with the lowest concentration of a local anaesthetic and narcotic mixture, so as to maintain motor function. A midline approach decreases the chance of intravascular puncture with the epidural catheter.21 The extent of motor block should be assessed frequently, and these examinations should continue until after the anaesthetic has worn off and the catheter has been removed. In this way, if the patient develops a motor block out of proportion to what one would expect, or if the anaesthetist has a seemingly prolonged duration of action, the patient can be immediately assessed with magnetic resonance imaging (MRI) for the development of an epidural haematoma.22 If the patient has an epidural catheter placed and later develops a coagulopathy, the catheter should be removed only after the coagulation status is corrected. Most importantly, as demonstrated by the uncomplicated management of this patient with a rare and severe bleeding diathesis, multidisciplinary planning, coordination of care, and timely communication is crucial in ensuring a successful outcome.