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Research Article

PREGNANCY WITH MULTIPLE CLOTTING FACTOR DEFICIENCIES: MANY FACES OF DEVIL!

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ABSTRACT

We report the medical management of a 26-years-old primigravida with a history of recurrent bleeding disorders during childhood. A coagulation profile performed during the 6th month of pregnancy showed a prolonged activated partial thromboplastin time (aPTT) combined with a prolonged 1prothrombin time (PT). An investigation of the coagulation factors by mixing studies showed a deficiency of multiple clotting factors. A working diagnosis of multiple clotting factor deficiency was made. The bleeding risk was considered to be high. She went into spontaneous labor and her labor was carried out in high dependency unit under the care of a senior obstetrician, a hematologist and a hemophilia treatment specialist with therapeutic dose of vitamin k and adequate arrangement of crossed matched blood, FFPs, cryo precipitates, and platelets. A total of 14 FFPs were transfused, 7 during second stage of labor and 7 immediately post delivery. Labor and postpartum period was uncomplicated. She delivered a female baby weighing 2.8kgs.. At D10 post-partum, the patient was discharged uneventfully.

INTRODUCTION

In a women with bleeding disorder, pregnancy can pose significant threat of hemorrhage (ante partum, more importantly delayed post partum) leading to a lot of anxiety among both the obstetricians and the patient. Coagulation disorders in pregnancy can be classified broadly into two categories: clotting factor abnormalities and platelet abnormalities, which could be inherited or acquired. Clotting factors disorders can be caused by inherited deficiency of a single factor or deficiencies of more than one clotting factors grouped as Familial multiple coagulation factor deficiencies. Among these bleeding disorders, in general and particularly in pregnancy, platelet disorders are the most common cause and are usually acquired rather than inherited. Hemophilias are well known inherited bleeding disorder but are relatively rare. Most common inherited bleeding disorder being Von willibrand's disease. Familial multiple coagulation factor deficiencies is a rare entity in itself, and its occurrence in pregnancy is barely reported in the literature. Here, we are reporting the case of a 26 years old primigravida with history of repeated bleeding episodes since childhood and multiple blood transfusions, diagnosed to have multiple clotting factor deficiency. Antenatal period was successfully managed by an experienced obstetrician, in collaboration with ahematologist and she had a full term normal delivery without significant morbidity to the mother or the neonate.

CASE REPORT

A 26 years old primigravida born out of second degree consangious marriage with history of repeated bleeding episodes since childhood (in the form of heamarthorosis, petechia, bruising following minor trauma, bleeding gums, menorrhagia) and multiple blood transfusions, was registered at 6th month pregnancy in our tertiary care institute. She had a married life of 2 years, non consangiousmarriage and had spontaneous conception. Shehad excellent dates confirmed by dating scan at 5-6 weeks GA. A targeted scan at 5th month ruled out obvious fetal anomalies. Folic acid, Fe and Calcium supplement were taken and was immunized with 2 doses of Tetanus toxoid. Her past menstrual cycles: regular/ 6-7 days/ 30 days, heavy flow, changing 3-4 fully soaked pads, with passage of clots. She had H/o spontaneous petechia, easy bruising following minor trauma, 2 episodes of swelling of joint following fall (suggestive of heamarthorosis) and bleeding gums. She had consulted local doctors and was managed symptomatically and received multiple blood transfusions for anemia and severe abdominal pain (?GI Bleeding).She had undergone a few blood tests and was diagnosed to have a clotting disorder and referred to our hospital, a tertiary care center for management of pregnancy. No significant finding was detected on general physical examination. Obstetric examination was normal, suggestive of live singleton fetus appropriate for the period of gestation. Her laboratory work up was as follows: Hemoglobin :11.7 gm%;Platelet count: 1,91,000 cells/ cu mm; Bleeding time: normal; Clotting time:

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prolonged; Prothrombin time: Control: 11.20 secs, test: 38.6 secs, INR:3.58,Ratio:3.44; APTT: Control: 28.80 secs, Test: 106.90 secs, Ratio: 3.71(significantly prolonged);Thrombin time: Control: 13.10 secs,test:26 secs, Ratio: 0.54;Serum fibrinogen: 120 mg/dL;D- dimer: 100 mg/L.Factor VIII C assay was performed in view of prolonged APTT and clotting time: 88.7% (Normal).Mixing study was carried out : V2 pooled N plasma + V2 patient plasma: PT: 13.1, INR: 1.14,APTT: 32.1; V2 absorbed plasma + V2 patient plasma, PT: 15.2, INR: 1.33, APTT: 38.8- Suggested likely factor VII, X, II deficiency.

A working diagnosis of multiple factor deficiency was made. She was admitted at term for maternal and fetal surveillance. She was treated with Vit K in therapeutic dose. She went into s pontaneous labor and her labor was carried out in high dependency unit under the care of a senior obstetrician with adequate arrangement of crossed matched blood, FFPs, cryoprecipitates, and platelets. A total of 14 FFPs were transfused, 7 during second stage of labor and 7 immediately post delivery. Labor and postpartum period was uncomplicated. She delivered a female baby weighing 2.8kgs.Her post delivery investigations were as follows: Hemoglobin :12.5 gm%;Platelet count: 1,90,000 cells/ cu mm; Prothrombin time: Control: 11.20 secs, test: 34.2 secs INR:3.16,Ratio:3.05;APTT: Control: 87.6 secs, Test: 28.80 secs, Ratio: 3.04;Serum fibrinogen: 190 mg/dL.

DISCUSSION

Familial multiple coagulation factor deficiencies are characterized by the inherited deficiencies of more than one plasma coagulation factor. To date, the genetic defect in two of these have been characterized: Combined deficiency of factor V and VIII and Combined deficiency of vitamin K–dependent clotting factors. Combined deficiency of Factor V and factor VIII is a rare inherited autosomal recessive disorder characterised by deficiency of Factor V and factor VIII. It is caused due to mutation in the gene MCFD2, which encodes a soluble luminal protein with two calmodulin-like EF-hand motifs at its C-terminus. This protein forms a complex with LAMN1 (lectin mannose binding protein 1; also known as ERGIC-53) that facilitates the transport of coagulation factors V and VIII from the endoplasmic reticulum to the Golgi apparatus via an endoplasmic reticulum Golgi intermediate compartment (ERGIC 53). Mutations in this gene cause combined deficiency of FV and FVIII, characterized by mild to moderate bleeding like epistaxis, menorrhagia, and excessive bleeding during or after trauma and coordinate reduction in plasma FV and FVIII levels. Plasma levels of coagulation factors V and VIII are in the range of 5 to 30% of normal andexhibits 5% residual clotting activity(1). Combined deficiency of vitamin K–dependent clotting factors-II, VII, IX, and X (and proteins C, S, and Z) is an extremely rareautosomal recessive disorder with fewer than 30 reported cases. Gamma glutamylcarboxylase is required for the activation of Vit K dependent clotting factors. This disorder is caused due to mutations in VKCFD1, which is associated with point mutations in the γ-glutamylcarboxylase gene (GGCX), and VKCFD2, which results from point mutations in the vitamin K epoxide reductase gene (VKORX). It is characterized by mild or severe bleeding and is associated with 1-30% residual clotting activity. The therapy includes high oral doses of vitamin K for prophylaxis, usually resulting in partial correction of factor deficiency, and episodic use of plasma infusions(2).In this case, there was prolonged clotting time suggestive of clotting factor deficiency and prolonged aPTT suggesting deficiency of factors of the intrinsic pathway. Test for VIIIC, which is the most common deficiency showed borderline activity, and mixing study suggested deficiencies of clotting factors VII, X, II. Thus this case is likely to have multiple clotting factor deficiency either Combined deficiency of factor V and VIII or Combined deficiency of vitamin K–dependent clotting factors. Genetic testing for the above mentioned known mutations could have confirmed the diagnosis.

CONCLUSION

Several bleeding disorders are characterized by the inherited deficiency of more than one plasma coagulation factor. To date, the genetic defects in two of these diseases have been characterized – ERGIC-53 gene leading to deficiency of factor V and VIII and VKORC1 gene leading to deficiency of vitamin dependant clotting factors. Pregnancy with coagulation disorder areassociated with significant risk of bleeding. Pregnancy, delivery and the puerperium should be managed by a multidisciplinary team, which includes obstetricians, haematologists and anaesthetists. A working diagnosis needs to be established after carrying out the necessary coagulation studies and testing for the specific clotting factor deficiency. Adequate blood products needs to be arranged to deal with the bleeding complications. To ensure coordinated prenatal and postpartum care, team effort is needed including specialists in high-risk obstetrics, a haematologist, in consultation with haemophilia treatment specialist.

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