IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 9 Ser.9 (September. 2019), PP 31-33
www.iosrjournals.org

Factor Xi Deficiency– Management in Adverse Conditions Case Based Learning

Dr.UzmaShaikh[1],MBBS,MRCOG senior specialist Obs/gyn, Al Corniche Hospital Abu Dhabi .UAE,
Dr.ZoqeenAkter[2],MBBS,MRCOG senior specialist Obs/gyn, Al Corniche Hospital Abu Dhabi .UAE,
Dr.NageenaMahmood,MBBS,MRCP consultant Obs/physician, Al Corniche Hospital Abu Dhabi .UAE,
Dr.Aqeela Mustafa[4]MBBS,MRCOG,[4]*Obs/gnae consultant hi-tech Sia Healthcare Center, Dar Es Salaam, Tanzania*

Dr. Mehar Fatima[5],MBBS,,*Senior medical Practitioner Obs/GynaeBuraimi Hospital Oman*
Dr. Habiba Omer Shaikh[6],MBBS,[8]*Rashid Hospital Dubai,UAE*

[1]*Editor in Chief, IOSR journal of dental and medical sciences (IOSR-JDMS)*
International Organization Of scientific research (IOSR)
Corresponding Author: Dr. Adiabbasi,Thailand

Abstract:*Factor XI deficiency is an uncommon disorder and is rarely encountered during pregnancy. However correct diagnosis, appropriate management planning and multidisciplinary collaboration is required to have successful outcomes. Although rare but tertiary obstetric care centers have to be well versed in the care of these cases.*

Date of Submission:05-09-2019 Date of Acceptance: 20-09-2019

I. Introduction

Factor XI (FXI) is an important component of the coagulation cascade and although its deficiency is uncommon but when such cases are encountered in routine obstetric practice it is imperative that the obstetrician is well versed with the management. We are presenting a case report of a pregnancy with FXI deficiency followed by a discussion on the recommended management and a comparison to our management when resources are a limitation and where unexpected circumstance leads to an altered management.

II. Case Review

A 25 years old primigravida, who was a known case of FXI deficiency, booked with us in clinic at 8 weeks gestation. She was an Emirati national and this was a non-consanguineous marriage. At booking at 8 weeks of her gestation she gave us a history of excessive bleeding during minor cuts and dental extraction however she had no history of menorrhagia. Family history was unremarkable and spouse was not affected. Routine booking bloods were done along with coagulation profile (and FXI levels done later when abnormal clotting corrected by mixing with controlled . Significant findings were Hemoglobin 14.2 gm/dl, Platelets 206 x 103, normal prothrombin time (PT) of 13.9 seconds, prolonged Activated Partial Thromboplastin Time (APTT) of 47.6 seconds (normal 27-42 seconds) and FXI levels done after abnormal APTT which was corrected after the repeat coagulation mixed with controlled plasma was found to be low that is 40 IU/dl (normal levels range from 70 -150 IU/dl).

Patients with hematological disorders are seen at our hospital in a joint clinic with a Consultant Obstetrician, Consultant Obstetric Medicine Physician and Consultant Hematologist, here the plan of care is agreed upon and documented in the file. This patient had regular visits to the joint clinic and her antenatal period was uneventful. Since FXI concentrate is not available, labor management plan was to give 2 units of Fresh Frozen Plasma (FFP) in active labour, 2 units after delivery and to review her on second day of delivery for further transfusion.,as well as for active management of 3rd stage of labor. Other instructions were to avoid instrumental delivery and fetal blood sampling, avoid epidural anesthesia, active management of third stage of labour , intramuscular injections and Non-Steroidal Anti Inflammatory Drugs (NSAIDS).

The patient presented with Spontaneous Rupture of Membranes (SROM) at 37+1 weeks gestation. She was positive for Group B Streptococci (GBS) hence immediate induction of labor was commenced with syntocinon infusion as per policy along with GBS prophylaxis. Once in active labor FFP was commenced as per

the documented plan and immediately she developed a transfusion reaction with itching and rashes all over her body which was managed accordingly and transfusion stopped. Following 7 hours she was 6 cm dilated hence after consultation with the multidisciplinary team it was decided to transfuse 2 units of FFP under cover of antihistamines and hydrocortisone. She developed a second reaction hence FFP was discontinued and decided not to transfuse any more . She progressed to normal delivery with a second degree tear after laboring for --thirteen-- hours. Total estimated blood loss was 400 ml. Observation in the labour ward was continued and Intravenous oxytocin infusion was commenced with regular monitoring of vital signs which remained normal. Post-delivery she was given Tranexamic acid 500 mg IV every 6 hours. Five hours after delivery she complained of rectal pain and a feeling to defecate. Local examination revealed a vaginal wall hematoma of 3 cm not in relation to suture line which was compressible. Decision of conservative management was made with Vaginal packing was done, antibiotics commenced and patient was observed in the High Dependency Unit (HDU) with a plan to repeat Hemoglobin in 6 hours.

On the second day the pack was removed and there was no change seen in the hematoma size. Although there was 1gm of drop in hemoglobib but she remained clinically stable. The hemoglobin remained stable after delivery. Patient was shifted out of HDU. On day 5 she had an episode of heavy vaginal bleeding which upon examination revealed spontaneous rupture of the hematoma. Since she was complaining of persistent dizziness 2 units of whole blood were transfused successfully under cover of antihistamines and steroids without any transfusion reaction signs and symptoms. She was discharged home on Day 7 in good condition.

III. Discussion

Factor XI deficiency is also known as Hemophilia C, Plasma thromboplastin antecedent deficiency and Rosenthal syndrome. It was first recognized in 1953. Factor XI is the zymogen of a blood coagulation protease Factor XIa that contributes to hemostasis through activation of factor IX[i] which in turn sustains thrombin generation and consolidates coagulation. This mechanism is important in tissues with robust fibrinolytic activities like the oropharynx and urinary tract.

Incidence:

The incidence is 1 in 1,000,000 in the general population. In North America the quoted incidence is 1 in 100,000 however it is most common in Ashkenazi Jews who have an approximate carrier rate of 5 in 100 for heterozygotes and 1 in 450 for homozygotes. It is also seen in Iraqi Jews.

Genetics:

Most of the cases are congenital with autosomal inheritance. Rarely it may present later in life due to liver disease and acquired alloantibodies to FXI via blood products. [ii]

The inheritance pattern is both recessive and dominant.[iii] The gene responsible is on the long arm of Chromosome 4. Two mutations of the genes are common and account for 90% of the cases however more than 180 mutations have been recognized making prenatal diagnosis difficult.[iv] Being an autosomal inherited disorder males and females are equally affected.

Pathophysiology:

The protein is synthetized in the liver and is a dimer. Normal dimerization is required for secretion of FXI from the producing cell. Hence mutations can be due to

1) Decreased synthesis of protein with no FXI production in the homozygous state

2) Abnormal dimerization of the protein producing 10% of FXI in the homozygous state

3) Dimerization which results in poor secretion with no measurable FXI in the homozygous state and a measurable factor XI that is lower than the expected in 50% in the heterozygous state. This third group is thought to explain the dominant mutation patterns that are seen in some families with FXI deficiency. [v]

Clinical Presentation:

Congenital FXI deficiency is a variable presentation from mild to moderate bleeding. It presents as menorrhagia, bleeding with dental extractions, circumcision and a laboratory finding of Prolonged APTT. The bleeding tendency varies in the same individual.[vi] Normal levels of Factor XI range from 70 – 150 IU/dl. Patients with severe deficiency have levels <15 IU/dl and those with partial deficiency have levels ranging from 15 – 70 IU/dl .[vii]

Management during pregnancy and labour

Management starts preconception when the severity of the disease is assessed, appropriate vaccinations discussed as the patient may need blood product transfusion and genetic consequences discussed with the

couple. Factor XI levels do not rise in pregnancy.[viii] The FXI levels are checked at booking, 28 and 34 weeks and prior to any invasive procedure. The 28 week levels are useful in those cases which may end up in preterm delivery. These patients are ideally managed in a multidisciplinary setting with involvement of a hematologist. An antenatal assessment by the anesthetist is also required as regional anesthesia is preferably avoided.

During labour take sample for group and save, full blood count and coagulation. For those deficient maintain IV line and give prophylactic treatment in the form of FXI concentrate, Recombinant Factor VIIIa , FFP and tranexamic acid. Recombinant products are the treatment of choice to avoid viral transmission . Since regional anesthesia and intramuscular analgesia is to be avoided during labour pain management options are markedly reduced. In certain cases with normal FXI levels after consideration of the risk benefit ratio regional anesthesia by an expert anesthetist can be considered and the catheter is to be removed only if the levels are normal or under cover of prophylactic agents or factor XI transfusion.

Invasive fetal monitoring during labour and instrumental delivery are not recommended. There should be an early recourse to Caesarean delivery in cases where progress is slow. However a low forceps delivery is less traumatic than a Caesarean section done with a deeply engaged head. Once the baby is born cord blood is to be collected to determine FXI levels and coagulation studies. Intramuscular injections are avoided and Vitamin K is administered orally

These patients are at an increased risk of primary and secondary PPH 16 and 20 % respectively as compared to the general population risk where the risk is 5 and 0.7 %.[ix]Having said that, other obstetric causes of hemorrhage should not be overlooked. Third stage should be actively managed and prophylactic administration of oxytocin infusion should be considered. Post-delivery the aim is to maintain FXI levels for 3 days after normal and 5 days after Caesarean delivery.

Thromboprophylaxis use is a difficult decision and should be done in concert with a multidisciplinary team as FXI concentrate is prothrombotic hence a calculated approach should be taken. Use of tranexamic acid with FXI concentrate is also avoided (due to high risk of thrombosis).

IV. Conclusion

Although Factor XI deficiency is a rare condition but maternal and perinatal morbidity and mortality can be deferred in cases where it is recognized and appropriate management is instituted. In many places not all resources are available. Our case shows use of alternatives in a patient who had an adverse reaction to FFP and where FXI concentrate was not available. Despite the challenges faced all decisions taken were by a multidisciplinary team and this is should be encouraged in all settings.

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Dr. Adiabbasi,Thailand. "Factor Xi Deficiency– Management in Adverse Conditions Case Based Learning." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 9, 2019, pp 31-33.