



Case Report

Management of mild congenital deficiency of Factor XI with a Factor XI inhibitor in pregnancy: A clinical case

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ARTICLE INFO

Article history:

Received 13 October 2020

Accepted 7 January 2021

Available online 13 February 2021

Introduction

Factor XI (FXI) deficiency is a rare congenital bleeding disorder that is more commonly found in Ashkenazi Jews and first described in 1955. Its transmission is autosomal recessive; homozygotes have FXI levels of < 20%, while heterozygotes have levels of 20–60% of normal (normal range 50–150%). However, there is evidence of bleeding even in heterozygote patients suggesting that transmission is not completely recessive.¹ This variability of bleeding tendency independent of the FXI level is more pronounced in non-Jewish kindred and presents a challenge in the management of pregnant patients.¹

Deficiency of FXI is important in that while spontaneous bleeding is uncommon it can cause prolonged or excessive bleeding following, trauma, abortion, postpartum and with the use of regional anaesthesia.² Only anecdotally have cases of immune mediated development of autoantibodies

against FXI in patients without a congenital deficiency been reported. However, its presence is potentially life threatening and has been associated with malignancy, autoimmune disorders, pregnancy, multiple transfusions or idiopathic.³ In patients with congenital Factor XI deficiency, inhibitors have been reported in patients with a severe deficiency and treated previously with plasma.³

We present the case of a 17-year woman who was diagnosed with mild congenital Factor XI deficiency at the age of four years and developed antibodies to FXI during her first pregnancy and her subsequent management.

Clinical case

A 17-year-old woman presented to her local hospital with an 8-week pregnancy. Her previous medical history included excessive menstruation since menarche, excessive bleeding following dental extractions and a tonsillectomy and ade-

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<https://doi.org/10.1016/j.htct.2021.01.003>

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noidectomy at the age of 4 years and appendectomy at the age of 13 years that required transfusions of fresh frozen plasma (FFP). There was no family history of bleeding disorders and she was receiving no medication.

Blood tests carried at the age of 4 years showed a Prothrombin time (PT) of 74% (normal range 70–100%), an Activated Partial Thromboplastin Time (APTT) of 49 s (normal range 25–34 s), a platelet count of 277,000/mm³ and a bleeding time of 6 min (normal). The APTT corrected with a mixture 1:1 with normal plasma, specific coagulation factor assays were normal except for Factor XI of 36% (normal 50–150%). The patient was diagnosed as having a mild Factor XI deficiency and had been treated with FFP for the two surgeries.

The patient was referred to our hospital at 12 weeks of pregnancy, the repeat blood tests showed a PT of 80%, APTT of 55 s, a platelet count of 238,000/mm³ and a bleeding time of 5 min. The APTT showed correction with a 1:1 and 1:4 mixture of normal plasma with no incubation, and following an incubation of two hours at 37 °C, a partial correction with a 1:1 mixture with normal plasma of 50 s and complete correction with a 1:4 mixture with normal plasma. A diagnosis of an inhibitor was made in addition to the mild deficiency of Factor XI. Tests for lupus coagulation using the Dilute Russell's Viper Venom test, antibodies to cardiolipins and beta-2-glycoprotein were negative. Factor XI assay showed a level of 30% with the presence of a low level FXI inhibitor using the Bethesda method of 1–5 Bethesda units.

Her pregnancy was uneventful until labour, where due to foetal distress the patient underwent emergency caesarean section. The APTT the day prior to admission was 49 s, PT 85%, a bleeding time of 6 min and a fibrinogen level of 573 mg/dl (normal range 200–400 mg/dl). Two units of fresh frozen plasma (FFP) immediately before and two hours after surgery combined with eight hourly oral tranexamic acid 500 mg for seven days was given to achieve haemostasis. The APTT after two units of FFP shortened to 35 s (normal). After the two units of FFP post-surgery the APTT was 32 s, with total correction with 1:1 normal plasma (32 s) and 1:4 (31 s). Carbetocin and methylergonovine were used posterior to the caesarean section to stimulate uterine contraction. A general anaesthesia was used and no haemorrhagic complications ensued. In the six weeks post-partum there were no haemorrhages, although the wound was complicated by a non-haemorrhagic seroma.

Discussion

Optimum obstetric management in women with FXI deficiency requires awareness of possible bleeding complications and a multi-disciplinary approach is recommended for the management of pregnancy and delivery.⁴ Bleeding risk does not correlate well with FXI levels and during pregnancy changes in other coagulation factors especially Factor von Willebrand and FVIII affect this risk.⁴ This is independent of any obstetric factors that may increase the bleeding risk. The APTT of 49 s the day prior to delivery is in line with this change, although these changes failed to completely correct the APTT.

Normal pregnancy is associated with a hypercoagulable state, with a progressive hormonally induced rise in coagulation factors VII, FVIII, FIX, fibrinogen and Factor von

Willebrand especially in the third trimester. The increase in these factors may shorten the APTT and may decrease the need for replacement therapy.⁴ This is accompanied by a decrease in the natural anticoagulants, Protein S activity levels and an acquired resistance to Protein C. FXI levels are unaffected by pregnancy but increasing levels of Factor von Willebrand during pregnancy decreases the risk of primary post partum haemorrhage in FXI deficient women. As the levels of Factor von Willebrand show a significant decrease by day 3 postpartum, patients with Factor XI deficiency typically present with secondary postpartum haemorrhage 6–9 days after delivery.⁴

The case is unusual in that in combination with a congenital deficiency of FXI, the patient had developed a low titre inhibitor to FXI. In patients with severe deficiency of FXI treated with plasma there are cases reports of the development of FXI inhibitors, an immune response to the presence of a “new protein” which is seen in other severe congenital coagulation deficiencies.³ This case is unusual in that the congenital deficiency was mild and as such circulating FXI was present although at lower levels. In patients with autoimmune disease, cancer or pregnancy the formation of an inhibitor thought to be related to immune dysfunction with aberrant rupture of the tolerance to FXI.³

The clinical history is important in determining whether or not a patient is a “bleeder” or “non-bleeder”. If two of the six following criteria are positive the patient is classified as a “bleeder”; bruising tendency, mucous membrane bleeding such as epistaxis, haematuria or GI bleeding, menstrual bleeding requiring treatment such as oral contraceptive, tranexamic acid or surgical procedure, bleeding post surgery, post dental extraction or in relation to parturition.¹ Using such criteria 48% of patients with levels of FXI between 15–70% (classified as mild to borderline) were classified as “bleeders”.¹ The patient reported here was positive for three criteria and thus classified as a “bleeder”. The risk of bleeding is also associated with the site of injury; if a site with high fibrinolysis is involved the risk of haemorrhage is increased up to 40% when compared to that at sites with low fibrinolysis.⁵ Bleeding symptoms of acquired FXI deficiency are even more poorly related to residual FXI levels, they range from absent or mild to life threatening and fatal haemorrhage,⁶ especially in related to parturition or surgery.

As such deficiency of FXI, both congenital and acquired are associated with increased primary and secondary postpartum haemorrhage in comparison with the general population, 10–22% versus 5–8% for primary and 7% versus 0.8% respectively.⁶ In women with mild Factor XI deficiency post partum haemorrhage after vaginal delivery was not significantly different from normal women, however it was significantly increased after caesarean delivery especially in women with a prior history of haemorrhage.⁷

Management antenatal includes the measurement of factor XI levels during the first and third trimesters and reviewed in a joint obstetric/haematology clinic to decide on appropriate haemostatic prophylaxis for labour and delivery. The type and duration of therapy should be individualized for each patient and based on the previous bleeding history and current haemostatic parameters. Obstetric management includes the use of alternative analgesia such as nitrous oxide and intramuscular injections should be avoided. Regional analgesia can

be used when combined with prophylaxis and the coagulation defect corrected. Active management of the third stage of labour using oxytocin in combination with ergometrine to expedite placental separation and to minimize genital trauma at vaginal delivery is recommended. Additional prophylactic uterotonic agents such as oxytocin infusion, ergometrine and oral misoprostol should be considered if additional obstetric risk factors are present.

Haemostatic prophylaxis has been reported to be used in 10–20% of reported cases.^{2,4} This includes tranexamic acid, from day –1 to +6, this may be particularly effective in patients with Factor XI deficiency as the uterine-placental interface is an area of increased fibrinolysis.⁴ It has been suggested that in patients with a FXI level <70 IU/dl tranexamic acid should be used as prophylaxis.⁷ FFP 10–20 ml/kg has been used to correct the coagulation deficiency, noting that there are risks of volume overload and hypersensitivity reactions and that it is not virally inactivated. It has been suggested that FFP should be used in patients with a FXI level of < 40 IU/dl, a bleeding history, caesarean delivery and neuraxial anaesthesia.⁴ In some countries plasma derived FXI concentrate or solvent detergent treated FFP are available, their use is efficacious and safe but physicians should remain aware of possible thrombotic complications.⁸ The aim is to achieve FXI levels of 30–45 IU/dl during the peri-partum period.⁸

In patients with low levels of FXI inhibitors higher doses of FFP or FXI concentrates may be sufficient to overcome the inhibitor effect, as was in this case report. In patients with higher inhibitor levels the use of activated prothrombin complex concentrates or low dose recombinant activated FVII (15–30 mcg/kg) every two to four hours.⁹ Experimental approaches include emicizumab, a bi-specific monoclonal antibody to FIX/FIXa and FX/FXa and mimic the function of FVIIIa cofactor on phospholipids. In severe FXI deficient plasma emicizumab produced a modest dose dependent coagulation function.¹⁰

Conclusions

Management of pregnancy in women with FXI deficiency requires a multidisciplinary approach and planned birth management based on clinical history and FXI levels. Prophylaxis is required especially for epidural anaesthesia and caesarean section. FFP remains first line treatment in many countries although is not virally inactivated, plasma derived FXI concentrate, solvent detergent treated FFP or aFVII avoid this but due to high costs may not be accessible in some countries. New

treatments such as emicizumab are being developed which may increase therapeutic options especially in those patients with high inhibitor levels.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

The authors wish to thank Mrs Ana Maria Palazuelos for her help in redacting the manuscript.

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