Prenatal diagnosis in factor XIII-A deficiency

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Abstract
Congenital factor XIII deficiency is a severe bleeding disorder that is inherited as an autosomal recessive trait. The condition is commonly due to absence of the factor XIII-A subunit protein in the plasma. The case of a baby is reported who showed typical clinical features of factor XIII-A deficiency, including recurrent bleeding from the umbilical stump and a life threatening haemorrhage after circumcision. Family studies were performed and molecular analysis, using a Short Tandem Repeat (STR) marker closely linked to the A subunit gene, allowed antenatal exclusion diagnosis to be undertaken in a subsequent pregnancy. The case highlights the importance of seeking a family history of bleeding disorders before surgery in the neonatal period, particularly if the parents are consanguineous. (Arch Dis Child Fetal Neonatal Ed 1999;80:F238–F239)

Keywords: factor XIII-A deficiency; prenatal diagnosis; autosomal recessive trait

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Case history
A baby was born at 39 weeks of gestation to a 21 year old primagravid woman of Pakistani origin. The parents were second cousins. One of the mother’s siblings had died in infancy as a result of superficial haemorrhaging from the penis following circumcision. Two further cousins were receiving treatment for factor XIII deficiency. There was also a family history of congenital adrenal hyperplasia.

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## Extracted Text

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STR and the mother (I) is heterozygous L1/L2. The affected proband (II) is L1/L1 whereas the fetus (II) is L1/L2—meaning that the mother’s normal allele has been inherited and the fetus is unaffected. A healthy boy was delivered at term and a normal factor XIII-A value of 94% was confirmed.

Discussion

Factor XIII deficiency is a severe bleeding disorder associated with impaired wound healing and an increased risk of spontaneous abortion in women. Twenty seven patients are currently registered with the haemophilia service in the United Kingdom, indicating a prevalence of about one case per two million of the population. Eighty per cent of affected infants present with recurrent bleeding from the umbilical stump. In the absence of replacement therapy, patients in later life frequently sustain superficial bruising, epistaxes, haematoma in muscles and joints, and intracranial haemorrhage. However, lifelong prophylactic treatment with plasma derived factor XIII concentrate prevents haemorrhagic complications. The half life of factor XIII is around 10 days and the concentrate is administered on a monthly basis at a dose of 10–15 units/kg.

Factor XIII circulates in plasma as a heterotetramer of two catalytic A subunits and two B subunits. Following activation by thrombin, the dimers disassociate and the A subunit catalyses the formation of covalent bonds between fibrin monomers and also between fibrin and other proteins including collagen, fibronectin, and α1 plasmin inhibitor. This cross linking generates a clot of high tensile strength which is more resistant to fibrinolysis.

In factor XIII deficiency the A subunit protein is usually absent and the B subunit deficiency has only been described occasionally. Missense mutations are most frequently detected with most amino acid substitutions located in the highly conserved catalytic core domain of the A subunit protein. Other defects, including microdeletions, frameshift, and nonsense mutations, are randomly distributed through the genomic sequence. If the location of the specific mutation is unknown, we have shown that the closely linked polymorphic marker HUMF13A01 can provide a valuable tool for gene tracking and accurate prenatal diagnosis. The size of this (AAAG)n tetra nucleotide repeat sequence can be rapidly and simply determined using PCR amplification. Previous studies have shown that the heterozygosity rate is around 75% in several ethnic groups and because it is located in the immediate 5' region of the gene, the risk of meiotic recombination is negligible. Kangsadalamppi et al have recently studied the segregation of the STR alleles in seven families with A subunit deficiency and showed that, in all cases, the inheritance of the mutated allele could be unequivocally linked to the STR marker.

This case highlights the importance of seeking a medical and family history of bleeding disorder in neonates before surgery. Haemophilia A and B are the commonest inherited coagulation disorders which may present with a severe haemorrhagic tendency in early life. However, rare autosomal recessive conditions including factor XIII deficiency, type III von Willebrand disease, and congenital afibrinogenemia may also be encountered, particularly in the offspring of consanguineous parents.

We are grateful to Dr PLF Giangrande of the Oxford Haemophilia Centre for his advice and assistance in the management of this case. The CVS was kindly performed by Mr M Selinger, Royal Berkshire Hospital. We are also grateful to Dr Linda Tyley, Southmead Hospital, Bristol, for assistance with fetal DNA extraction.


