Factor XIII Deficiency: Report of Two Cases

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Factor XIII deficiency is one of the rare clotting factor deficiencies. Although rare, it is an important disorder because of seriousness of its bleeding manifestations, in particular the incidence of intracranial hemorrhage is higher than any other bleeding disorder. Hence an early diagnosis is extremely important where bleeding manifestations can be prevented by prophylactic factor XIII replacement given at every 4-6 week interval. Case1 presents the management of a factor deficiency associated with a very rare blood group AB+ve, while the case 2 reports the successful surgical management with a replacement therapy.
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INTRODUCTION

FactorXIII is the last enzyme in coagulation cascade and is an essential component of normal hemostasis. It is also referred to as Loki-Lorand factor, fibrinase, protranscoagulase and fibrin polymerase.[1] Factor XIII is a zymogen present in plasma and on the surface of platelets, which after consecutive activation by thrombin and calcium, catalyses the covalent cross linking of fibrin molecules in the final step of blood coagulation.[2,3] The activated factor XIII is responsible for the formation of proper clot by cross linking fibrin monomers into polymers. This produces increased clot strength and resistance to fibrinolysis.[4]

The factor XIII zymogen circulates in plasma as a tetramer composed of two subunits: Subunit A has enzymatic activity, whereas subunit B acts as supporting unit. Congenital deficiency of factorXIII activity is an uncommon, autosomal recessive inherited bleeding disorder with an estimated incidence of one in 3-5 millions [5,6,7] The deficiency is an autosomal recessive pattern of inheritance and is caused by lack of enzymatic subunit A.[4,8,9,10] There have been over 200 cases of factor XIII deficiency in the international literature since its first description.[11]

The early manifestations of the disease occur in neonatal period with umbilical bleeding seen a few days after birth which is characteristic and a frequent finding. Incidence of intracranial hemorrhage has been reported to be 25-30% which is higher than in any other congenital bleeding disorders and is the main cause of death and disability in these patients. Echymosis, intramuscular bleeding, post extraction bleeding, mucosal hemorrhage are other manifestations. Even though the clot forms normally in these patients, it begins to break down 24-48hrs later because of weak cross linking of fibrin leading to subsequent episodes of bleeding[1,5,11]

The diagnosis of this severe disorder may be delayed, since all the standard routine laboratory tests such as Bleeding time, Platelet count and platelet function tests are all within normal limits. The abnormal urea clot lysis test is a simple screening test to detect factorXIII deficiency.[3] Preparations of Whole Blood, Fresh Frozen Plasma, Fraction I Of Cohn, Cryopricipitate and Fibrinogen have all been used in the treatment factor XIII Deficiency.[2, 11]

The present article documents the report of two rare cases of factor XIII deficiency and their successful management in our pediatric set up.

CASE REPORT

A 13 yr old boy reported to the Department of Pediatric Dentistry, College of Dental Sciences, Davangere, with a chief complaint of pain in lower right back teeth region. The pain was stabbing type with sudden onset, severe in intensity and was localized. The Pain was aggravated on chewing and relieved on medication. The Child's past medical history was significant, revealing prolonged umbilical bleeding 5

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days after birth. The blood investigations were unavailing and the condition remained undetected. The bleeding episode was controlled later by fresh blood transfusion. After a few years, when the child was around 5yrs, the condition was diagnosed as the factor XIII deficiency while treating an episode of heamarthrosis. The child had history of recurrent spontaneous bleeding into the joints(heamarthrosis) and frequent intramuscular bleeding after minor trauma. Such hemorrhagic episodes were managed by fresh blood transfusion or cryoprecipitate and twice with factor XIII concentrate. The Child's history was otherwise normal for bleeding from nasopharynx, oropharynx, urinary tract or rectum, nor was there reported hemoptysis,or hemetemesis. No history of cardiac, pulmonary, hepatic, splenic or adrenal diseases. All routine laboratory values for bleeding time, partial thromboplastin time, prothrombin time were within normal range. The blood group of the child is AB+ve which is also a rarest among all the blood groups.

The family history revealed that, his elder sister had died at an early age of 8 months. She had similar features of factor deficiency with prolonged umbilical bleeding at birth. His younger brother is also a known case of factor XIII deficiency in whom the severity of heamarthrosis is comparatively more pronounced and has been physically disabled due to repeated heamarthrosis of knee joint.The parents gave history of consanguineous marriage.

Intra oral examination of the child revealed a deep caries on 46. The tooth was tender for percussion with obliterated vestibule. The radiograph of the tooth revealed a radiolucency reaching the pulp (Fig1).

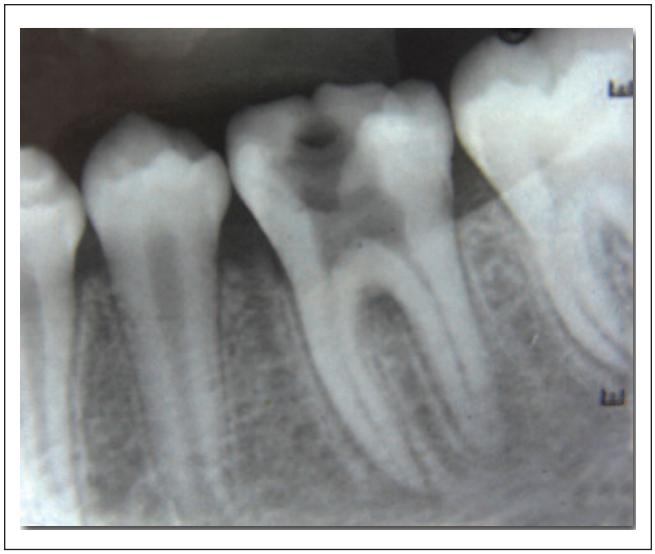

Figure 1. Deep caries involving pulp of 46.

The clinical and radiographic features were suggestive of an acute periapical abcess of 46. Root canal therapy was planned for 46. Immediate drainage was established through access opening of 46 and antibiotic and analgesics were prescribed. An openion of child's pediatrician was sought for further procedures to be carried out. The pediatrician furnished all details regarding child's condition and instructed to take utmost precautions and to carry out atraumatic procedure and also instructed to admit the child if at all any bleeding occurs The pulp was extirpated, working length was determined. Biomechanical preparation was done to the predetermined working length with utmost precaution to prevent any over instrumentation beyond apex. Obturation was carried out a week later followed by permanent restoration (fig2). The endodontic intervention was carried out successfully without any factor replacement.

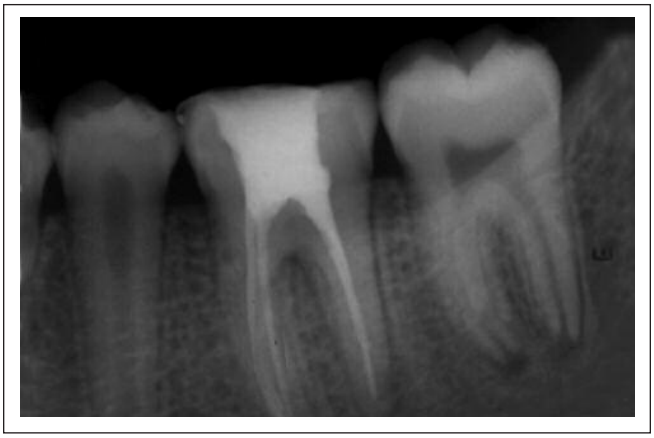

Figure 2. Obturation of tooth 46 without any factor replacement.

CASE REPORT 2

A 7year old boy reported to the department with a chief complaint of blood oozing out from the lower front teeth region. The medical history of the child revealed that, he was diagnosed of having factor XIII deficiency soon after birth when screened for the reason of uncontrolled umbilical bleeding. The child had fresh blood transfusions many times to treat such bleeding episodes. The family history of the child revealed that the elder brother also had similar bleeding manifestations and was also diagnosed of having Factor XIII deficiency.

The Intra oral examination of the child showed mobile tooth 72 associated with blood oozing from sulcus and root stumps of teeth 74 and 75 (Fig 3).

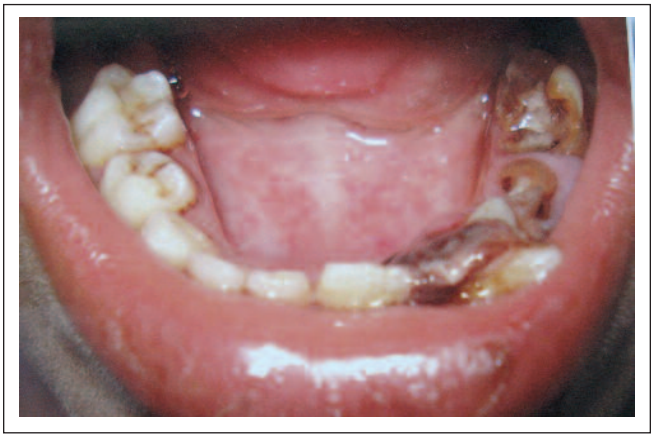

Figure 3. Blood oozing from tooth 72. Root Stumps of teeth 74 and 75,

Extraction of the mobile tooth 72 along with root stumps of 74 and 75 was planned and the child was referred for pediatrician's opinion.. As *per* pediatricians advice FXIII replacement in the form of fresh blood transfusion was carried out and the same day the extraction of all the three teeth were done under local anesthesia followed by the application of local hemostats. (Gel foam. Pfizer Pharmaceutical. U. S) The procedure was uneventful with normal clot formation and wound healing (Fig 4).

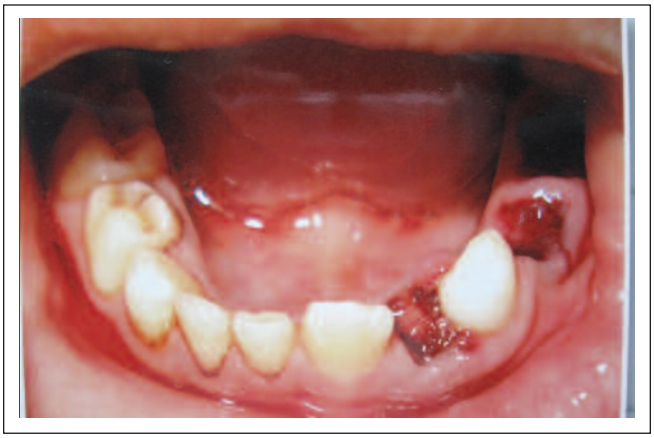

Figure 4. Normal clot formation and healing after extraction of 72,74,75

DISCUSSION

The factor XIII is not just another plasma protein in the clotting cascade. It is a fascinating clotting factor because of its peculiar features. Robbins first postulated the existence of factor XIII in 1944. In 1960, Duckert *et al* described the first recognized case of clinical bleeding diathesis due to congenital deficiency of this protein[12] Since its description, >200 cases of factor XIII have been reported of which very few cases have been reported in dentistry.[11] No racial or ethnic group is disproportionately affected. The factor XIII has relatively long half life (8.4days) compared to other factors, ex.Factor VIII..12hrs.[4,13,14] Only 0.5-2% of normal factor is sufficient to control minor bleeding episodes, whereas 30-35% is sufficient to control major episodes of bleeding.[4]

The factor XIII deficiency is associated with severe bleeding, spontaneous intracranial hemorrhage, poor wound healing and spontaneous abortions. Heterozygote patients can have reduced levels of FXIII-A and FXIII-B. and will usually be clinically asymptomatic. Hemorrhage of the umbilical cord and umbilical region has been reported as the first symptom in 90% of the cases of congenital factor XIII deficiency and is pathognomic. Hematoma formation in thigh due to intra muscular bleeding has been observed as initial incident.[4] Both of these features were prominent in our cases also. Incidence of intracranial hemorrhages is higher with factor XIII deficiency than with any other factor deficiencies and represent a significant threat to life. Patients have life long tendency to bleed into skin, subcutaneous tissue and muscle. Female sufferers are unable to carry a pregnancy to full term and suffer recurrent miscarriages.

Factor XIII deficiency is marked by normal coagulation screening tests despite a convincing history of bleeding. The most useful assays for factor XIII deficiency exploit the solubility of non-crosslinked fibrin clots in 5M urea or weak organic acids. Clots formed in factor XIII deficient plasma are soluble within minutes in such solutions, whereas normal clots remain insoluble for ≥24 hrs. The test of solubility in 2% acetic acid is said to be more specific for factor XIII deficiency. Other tests for factor XIII activity use measurements of incorporation of fluorescent amino acids into casein or ammonia production by the amilase activity of factor XIII.[12,15] In the present case1, the factor deficiency was diagnosed at the age of 5yrs by clot stability test and later it was confirmed by factor XIII assay. And in case 2 it was confirmed a few days after birth.

Preparations of whole blood, factor XIII concentrate, Fresh Frozen Plasma, Fraction I of Cohn, Cryopricipitate and Fibrinogen have all been used in the treatment factor XIII Deficiency.[2] The treatment of choice is plasma-derived FXIII concentrate that is pasteurized to provide virologic safety and is less likely than plasma to cause systemic reactions. Recombinant FXIIIA2-concentrates are currently being evaluated in clinical trials. In the present cases both children have received fresh whole blood transfusions most of the times and factor XIII concentrate only twice.

The preoperative prophylaxis, intra operative management, and post operative care are all equally important in the management of any case of bleeding disorder. A single infusion of fresh frozen plasma concentrate is sufficent to carry out dental extractions and minor surgical procedures in FXIII deficiency.[4] In the present case 2, single unit of factor XIII concentrate was infused 1hr prior to extraction but no pre-operative prophylactic infusion was carried out in case 1. The local hemostatic procedures are some times more important than replacement therapy.[2] Unlike other clotting factors, multiple infusions and the addition of Epsilon amino caproic acid to the regime are not needed since the half life of the FXIII is very long.

Factor XIII deficiency is inherited as an autosomal recessive trait. Heterozygotes are not affected with bleeding, although it is thought that heterozygous women may have higher incidence of spontaneous abortions than do normal women.[12] Congenital factor XIII deficiency can be due to defect in either F XIII-A gene or FXIII-B gene. The gene for the A subunit is reported to be present at 6P24,25, near HLA locus. The gene for the B subunit is located at 1q31-32.1[12] Bleeding disorders due to mutations in FXIII-B gene occurs infrequently. This rare bleeding disorder affects people of all races and there is often a history of consanguinity within certain families of FXIII deficient patients. The first published genetic mutation leading to factor XIII deficiency was reported by Webb et al in 1992. With the advance in biotechnology, more than 70 factor XIII A or B subunit gene mutations have now been identified. To date there are only 4 known mutations for FXIII-B leading to more rare form of F XIII deficiency.[1]

CONCLUSIONS

Factor XIII deficiency is unique. The early diagnosis plays a key role in the successful management of the condition. Serious bleeding manifestations associated with the condition can be completely prevented by prophylactic factor XIII concentrate. There are few clotting disorders where prophylaxis is so important and so effective. In view of high risk of intracranial hemorrhage it is now recognized that all patients with factor XIII deficiency should be offered prophylaxis from the time of diagnosis. The dental management of the condition is similar to other clotting disorders. Pediatric dentist should not confine himself in rendering the dental therapy to these patients but also should create a positive attitude in patients and parents in facing inherent complications associated with the condition.

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