Factor XIII Deficiency in Siblings: Importance of Prophylactic Replacement

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Abstract Factor XIII deficiency, an autosomal recessive trait, can result in serious bleeding manifestation. This case report presents two brothers with Factor XIII deficiency. Though the younger sibling had been screened and diagnosed prophylactic replacement therapy had not been initiated unlike the elder brother. He presented with intracranial haemorrhage needing surgical evacuation while the elder brother remained symptom free on regular prophylactic replacement of FFP.

Introduction

Congenital factor XIII deficiency is a severe bleeding disorder that is inherited as an autosomal recessive trait [1]. Since it was first reported in 1960, more than 200 cases have been reported worldwide [2, 3]. Factor XIII plays an integral role in hemostasis by catalyzing the cross linking of fibrin, platelet membrane and matrix protein throughout thrombus formation thus stabilizing the blood clot.

The molecular basis of factor XIII deficiency is characterized by a high degree of heterogeneity which contributes to the different clinical manifestations of the disease varying from mild bruising to life threatening hemorrhage. The case of two siblings is reported who showed typical clinical features of factor XIII-A deficiency, including prolonged bleeding from the umbilical stump and life threatening haemorrhages. The case highlights the importance of screening family members and need for prophylactic replacement.

Case Report

A 14-year-old boy born of a second degree consanguineous marriage presented with a history of headache and vomiting since 2 days and blurring of vision. At admission he was well oriented, had a GCS of 15/15 with no evidence of any focal deficit. After 6 h of admission, he had worsening of sensorium with loss of vision with bilateral papilloedema. CT Head was suggestive of intracranial bleed (Fig. 1). Neurosurgery opinion was sought and he was taken up for surgery under cover of fresh frozen plasma. He underwent right parieto-occipital craniotomy with evacuation of intracerebral hematoma.

Past history of this child revealed a history of prolonged bleeding from the umbilical cord in the neonatal period which required surgical intervention. Though he had minor skin bruises, which were managed conservatively with ice application, he had never received any transfusion. On further probing, it was learnt that his elder brother also had prolonged umbilical cord bleed in the neonatal period and a trivial trauma had resulted in an intra-abdominal hematoma at the age of 15. At that time both of them had been screened with haemostatic screening tests and diagnosed as factor XIII deficiency with urea clot lysis test. Their sister was also evaluated and her screening tests were negative.

The elder sibling was under regular FFP transfusions after his diagnosis, and was asymptomatic. However, the parents had deferred any replacement therapy for this younger child as he never had any major bleeds so far.

Following surgery the patient had left facial upper motor neuron palsy and left hemiplegia, which improved gradually. Histopathological examination of specimen revealed organizing hematoma with reactive gliosis. He has been under regular follow up 1 year post surgery and has no residual left facial nerve palsy. He is also receiving

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Fig. 1 CT head showing a nonenhancing hyperdense collection with a focus of increased attenuation in the right parieto-occipital hemisphere with surrounding hypodense area s/o parieto-occipital hematoma with acute hemorrhage within and mass effect

regular prophylactic plasma transfusions and has been asymptomatic.

Discussion

Factor XIII, the last enzyme in the coagulation cascade is essential for normal hemostasis. Circulating as a proenzyme composed of 2A subunits and 2B subunits, factor XIII requires calcium and thrombin for activation [4, 5]. Activated factor XIII A, a transglutaminase catalyses the formation of lysine and cross-links between fibrin monomers resulting in a fibrin clot that has greatly increased tensile strength. Although rare with an estimated incidence of 1 in 10^6 , congenital Factor XIII deficiency is one of the most severe hereditary bleeding disorders [3]. Patients have a lifelong tendency to bleed into the skin, subcutaneous tissues and muscles. Females with factor XIII deficiency are unable to carry a pregnancy to term and suffer recurrent miscarriages [6]. In a study the most common bleeding symptoms reported were subcutaneous bleeding (57%) followed by delayed umbilical cord bleeding (56%), muscle hematoma (49%), hemorrhage after surgery (40%), hemarthrosis (36%), and intracerebral bleeding (34%) [7]. The clue to diagnosis is the prolonged umbilical bleed found in 80% of patients. Our patient and his brother too had prolonged umbilical bleed. As delayed bleeding is common, history of trauma may be forgotten. Both brothers had skin and subcutaneous tissue bleeds. Both had life threatening bleeds, one an intra-abdominal hematoma, the other an intracranial hematoma. Timely diagnosis and intervention prevented mortality in both.

Because standard coagulation tests are normal, the diagnosis will be missed unless specific tests are conducted. The screening test for factor XIII deficiency is solubility of the patient's recalcified plasma clot in urea or monochloroacetic acid [8]. A definite diagnosis is then made on the basis of functional and immunologic assays. Our patient had already been diagnosed by screening. Unfortunately it did not change the course of events as the parents chose to ignore it.

The early diagnosis is important because serious bleeding manifestations 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 the high risk of intracranial hemorrhage, it is now recognized that *all patients with FXIII deficiency should be offered prophylactic treatment from the time of diagnosis* [9]. It has been suggested that FXIII levels of ~ 3 –10% of the normal population mean (0.03–0.1 IU/ml) are sufficient to prevent spontaneous hemorrhage [10]. As the half-life of endogenous factor XIII is long, ranging from 5–11 days, prophylactic therapy with fresh frozen plasma in doses of 10 ml/kg can be given every 4–6 weeks. Cryoprecipitate can be administered at 1 bag per every 10–20 kg every 3–4 weeks. Currently in the US, most patients are being treated with plasma-derived pasteurized factor XIII concentrates (Fibrogammin P; CSL Behring, Marburg, Germany). Both the siblings have been on FFP transfusion and have remained asymptomatic.

This case has been reported to underline the importance of screening and prophylactic replacement therapy once diagnosis is established, even in an asymptomatic child, as the first bleed could be potentially fatal. Replacement therapy is by transfusion of factor XIII concentrate/fresh frozen plasma/cryoprecipitate.

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