

CASE REPORT

Factor XIII Deficiency - A Case Report with Review of Literature

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ABSTRACT

Factor XIII deficiency is a rare disorder and these patients present with bleeding diathesis in the neonatal period. An 18 days old male child was brought with the history of umbilical stump bleeding. Two previous siblings had died in the neonatal period of an unknown cause, possibly because of intracranial haemorrhage and another at the age of 6 years of unknown cause. Investigations revealed Factor XIII deficiency. He was put on Fresh Frozen Plasma (FFP) support as he could not afford Fibrogammin and currently receives 6 weekly FFP and is doing well. *J Med Sci* 2009;12(2):53-55

Key words: Factor XIII deficiency, Bleeding diathesis, Fibrogammin.

Introduction

Factor XIII deficiency is a rare disorder. Patients having factor XIII deficiency, have a bleeding tendency of varying severity, major morbidity being spontaneous intracranial haemorrhage. factor XIII deficient patients usually bleed in the neonatal period from umbilical stump or circumcision. In addition affected males may have oligospermia and female patients may suffer recurrent miscarriages. Replacement therapy of factor XIII is highly satisfactory because of long half life and small quantities are needed to control the bleeding.

Case Report

18 days male child, fourth in birth order, product of consanguineous marriage referred to our Tertiary Care Institute with history of trivial umbilical stump bleed on day 10 for which patient had received injectable vitamin K without any relief. There was no history of abdominal pain,

purpura or bloody diarrhoea. Physical examination revealed no active bleeding or neurodeficit. Family history revealed that first female sibling of 6 years of age was apparently normal. The second and third siblings, both male babies died in the neonatal period possibly due to the intracranial haemorrhage.

Investigations revealed Hb 15.7g/dl (Normal 12 – 16 gms/dl), total leucocytic count $14.65 \times 10^3/\mu\text{L}$, differential count P36%, L48%, M11%, E5%, platlet count: $279 \times 10^3/\mu\text{L}$. Coagulogram revealed: PT 14 sec (control 12) PTT 26 sec (control 24) TT 18 sec (control 18) PTI 85.7% and INR 1.17. Bleeding Time 2 minutes, 2 seconds. Clot solubility test revealed lysis of the clot in 5M urea within 7 minutes.

Factor XIII levels were : 12 $\mu\text{g/ml}$ (normal 60 $\mu\text{g/ml}$) Patient received injection of fresh frozen plasma (single infusion) on the day of first contact itself, since then is on regular FFP support, currently receiving FFP at 6 weekly intervals.

Discussion

The existence of factor XIII was first postulated by Robbins in 1944 and in 1960, Duckert described the first recognized patient with a clinical bleeding diathesis due to

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congenital deficiency of this protein. Fibrin stabilizing factor was given the designation factor XIII in 1963. No racial or ethnic group is disproportionately affected, and the incidence is estimated at one in several million¹.

Factor XIII, a protransglutaminase, is a terminal enzyme in the coagulation cascade, and it functions to cross-link the fibrin clot, thereby stabilizing it against premature fibrinolysis.² Factor XIII circulates in plasma as a heterodimer with of a 340,000 Da molecular weight.³ Factor XIII stabilizes fibrin clots by forming ϵ -amino g-glutamyl cross links between adjacent a and b chains of fibrin. Factor XIII transglutaminase joins the g- carbon of glutaminase residue on one chain to the ϵ -amino group lysine in the other. Factor XIII is a 320,000 Mr glycoprotein composed of A and B subunits with a plasma half life of about 10 days. It is activated by thrombin in the presence of calcium.⁴ Hematopoietic cells constitute the principal site for biosynthesis of Factor XIII A subunit. The Factor XIII B subunit is synthesized primarily by hepatocytes.⁵ The B units function as carrier proteins, stabilizing the A subunits in circulation and regulating the non-proteolytic activation of Factor XIII.^{6,7} The cDNA and protein sequences of both subunits have been determined.^{8,9} Limited proteolysis by thrombin converts zymogen Factor XIII to the Factor XIIIa enzyme, which stabilizes the clot by catalyzing fibrin cross-linking. Although fibrin is the main substrate for Factor XIIIa, the molecule further contributes to the generation of a stable clot that is resistant to fibrinolysis by incorporating antifibrinolytic proteins such as α_2 antiplasmin in to the forming clot.¹⁰ Maintaining a sufficient plasma level of factor XIII is essential for normal haemostasis. Patients who have congenital factor XIII deficiency have a bleeding tendency of varying severity, the major morbidity being secondary to intracranial hemorrhage (ICH), which is more frequent in factor XIII deficiency than in other congenital bleeding disorders.¹¹ The bleeding associated with factor XIII deficiency is usually associated with trauma, except in the case of intracranial hemorrhage which may occur in the absence of known trauma. Intracranial hemorrhage is reported in up to 25% of patients in some series.¹² In the setting of congenital factor XIII deficiency, it generally has been accepted that plasma Factor XIII levels of 5% are sufficient to maintain hemostasis.

Several drugs including isoniazid, may bind to cross linking sites on fibrinogen and mimic Factor XIII deficiency by blocking enzyme activity, a single infusion of fresh frozen plasma of a purified factor XIII-rich product derived from a human placenta called fibroga-mmin is effective. Plasma factor XIII circulates in association with its substrate fibrinogen. Cellular factor XIII in platelets becomes activated through a non proteolytic process. Inherited deficiency is transmitted in an autosomal recessive manner. Factor XIII A chain has been localized to chromosome 6(p24-p25) whereas B chain has been

localized to chromosome 1(q31-q32.1). Parents of affected individuals are typically asymptomatic. Deficiency of the factor XIII A chain is the predominant abnormality and occurs at a frequency of approximately 1 in 2 million. (approximately 200 unrelated cases have been described). Missense mutations are the most common mutations of the Factor XIII a chain gene. Deficiency of α chain as a cause of F XIII deficiency has been reported only in 3 cases.¹³

Three forms of F XIII deficiency have been described. In type I deficiency, subunits A and B are lacking; in type II deficiency, the subunit A is lacking, but subunit B is present; in type III, the subunit B is lacking.^{14,15} Factor XIII α and β subunits can be quantified by immunological methods using commercial polyclonal antisera. Kits are now available for direct assays of factor XIII antigen.

Plasma factor XIII circulates in association with its substrate, fibrinogen. The key step in the activation of the plasma factor XIII thrombin cleavage of the Arg 37-Gly 38 bond in the A chain to release a Mr 4500 activation peptide. This leads to dissociation of A and B subunits and the exposure of active site on the free subunits. Factor XIII deficient patients usually bleed in the neonatal period from the umbilical stump or circumcision. Affected male patients may have oligospermia and female patients may have recurrent miscarriages. In addition to hemorrhage these patients may have poor wound healing. These observations suggest that the enzyme may be important in other physiological processes beyond haemeostasis including placental implantation, spermatogenesis and wound healing. Patients with factor XIII deficiency may have a higher incidence of intracranial hemorrhage than do patients with other inherited bleeding disorders. This is the basis for recommending prophylaxis against intracranial hemorrhage by regular replacement therapy. Echymoses, hematomas and prolonged bleeding from trauma are also characteristic. In some patients bleeding following trauma may be delayed for 12 to 36 hours, while in other patients immediate bleeding occurs. Haemarthroses and bleeding into muscles are less common, however, than in haemophilics.

Replacement therapy for factor XIII deficiency is highly satisfactory because of small quantities of factor XIII needed for effective hemostasis and long half life of factor XIII, which is approximately 19 days. Plasma derived, virus inactivated concentrate of Factor XIII are available and are the treatment of choice. Fresh frozen plasma can also be used where concentrates are unavailable. Transfusion of 2 to 3 ml of plasma per kilogram of body weight will produce hemostasis for periods of 4 weeks. Prophylactic therapy using infusions of plasma every 3 to 4 weeks has been successful in achieving normal hemostasis and preventing habitual abortions. Prophylactic therapy can even be accomplished by the use of FFP given as 1 or 2 units every 4 to 6 weeks.¹⁶ Factor XIII

concentrate (fibrogammin, Hoechst) are available in Europe, and have been used successfully in prevention of hemorrhagic complications.

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