

Case Report

Congenital hypofibrinogenemia: a case report

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ABSTRACT

Fibrinogen disorders are rare bleeding disorders. Fibrinogen is also called factor I which is involved in last step of coagulation cascade. Congenital hypofibrinogenemia is usually caused by mutation of FIB (fibrinogen-binding protein) gene. These disorders should be suspected when Thrombin time is prolonged in well look child with history of bleeding manifestations. We are describing a female child who is having pallor with history of recurrent ecchymosis and minor post traumatic bleeding. Based on coagulation screening profile, we made the diagnosis of hypofibrinogenemia.

Keywords: Fibrinogen, Bleeding diathesis, Congenital hypofibrinogenemia and children

INTRODUCTION

Congenital hypofibrinogenemia is a rare inherited hemostasis disorder characterized by deficiency and/or defect of fibrinogen.¹ Fibrinogen gene located on chromosome 4 short arm (q26-q28).² Fibrinogen is a coagulation factor I which is converted to fibrin clot in last step of clotting cascade. Hemostasis is the process of blood clotting when blood vessel injury occur.³ This disorder can be quantitative/qualitative. Quantitative includes hypofibrinogenemia and afibrinogenemia, and qualitative is a dysfunctional fibrinogenemia.²

Affected patients can present since neonatal period, ranging from asymptomatic and mild bleeding/post traumatic bleeding to life threatening spontaneous bleeding.⁴ Umbilical cord hemorrhage or prolonged bleeding from umbilical stump is often (85%) the first bleeding episode in patients with congenital afibrinogenemia.⁵ Afibrinogenemia usually present in early infancy than hypofibrinogenemia. Intracranial hemorrhage (ICH) is also a common site of bleeding in children with afibrinogenemia. Sometimes menorrhagia is the only symptom in adult female patients. These patients rarely can present with recurrent microbleeds in

hip joint, muscular hematoma and mucosal bleeding in childhood⁶. Female patients are vulnerable to menorrhagia, spontaneous recurrent abortion, antepartum and postpartum hemorrhage.⁷ The screening tests for fibrinogenemia includes prolonged PT, PTT and Thrombin Time but the diagnosis is confirmed by demonstrating decreased activity and/or low levels of immunoreactive fibrinogen (fibrinogen antigen) in plasma.⁸ Congenital hypofibrinogenemia is defined as a partial deficiency of fibrinogen 20-80 mg/dl of plasma. Congenital afibrinogenemia is defined as plasma levels below 10 mg/dl. Normal fibrinogen antigen levels are between 200 to 400 mg/dl.¹

CASE REPORT

A 7-year-old female child was admitted with chief complaint of easy fatigability for 2 weeks. Child had past history of spontaneous umbilical bleeding at 12 days of life in neonatal period. Again after 14 months of life, child had history of ecchymosis and prolonged bleeding with minor injuries. Child was given 2 blood transfusion till now. This child was a product of 3-degree consanguinity and no one had similar complaints in her family. On examination child was well nourished and had

pallor. No bleeding manifestation were seen. Systemic examination was absolutely normal with no organomegaly.

At 12 days of life in peripheral hospital, PT, APPT and INR were normal. Hb was 3.5 gm% and after transfusion it was 7.5 gm%. At 14 months of life, PT (32 sec), APPT (47.2 sec) and INR (2.6) were prolonged. (Hb was 8.2%, WBC 19300/ μ L and platelets were 6.4 lacs/ μ L). At present admission in our hospital, Hb is 5.7 gm%, WBC count-14000/ μ L and platelets-3.4 lacs/ μ L. PT (532.4 sec) and a APTT (600 sec) are prolonged. As suspecting bleeding disorder, we sent hemostasis screening profile which had shown that PT, APTT and TT were prolonged. Fibrinogen was 40 mg/dl (normal 200-400 mg/dl). Clot solubility test was abnormal. Factor XIII was normal level. Platelets and WBC were normal. These features are consistent with hypofibrinogenemia/dysfibrinogenemia. Immunoreactive fibrinogen estimation and genetic analysis not done due to financial constraints. Consent was taken for publication.

DISCUSSION

Patients with congenital hypofibrinogenemia often presents with bleeding manifestations such as ecchymosis, subcutaneous hematoma, mucosal bleeding and post traumatic bleeding since neonatal period. Our patient was presented with umbilical bleeding and ecchymosis. As coagulation factors will not cross placenta all coagulation and anticoagulation factors are less in neonates, particularly anticoagulation factors are lesser, that's why neonates are more prone to develop thrombosis than any other age. But the levels of the factors V, VIII, XIII, and fibrinogen are similar to adult values.⁹ Fibrinogen synthesis starts in fetal liver.

Post traumatic bleeding is less in hypofibrinogenemia than afibrinogenemia at birth because of von Willebrand factor backup fibrinogen by platelet aggregation and as both are acute phase reactants, levels usually increased at the time of birth. In our case we had prolonged PT, APTT and TT. Thrombin time and reptilase time are best screening tests to detect fibrinogen deficiency.¹⁰ The fibrinogen level was 40 mg/dl (200-400 mg/dl) and diagnosed as hypofibrinogenemia. The bleeding manifestations are depending on levels of fibrinogen, levels >100 mg/dl usually have no bleeding findings and levels >70 mg/dl have protected from spontaneous bleeding.¹¹

Acquired causes of hypofibrinogenemia like liver disorders and DIC ruled out by normal LFT and platelets. In our case we had abnormal clot solubility test which is a screening test for factor XIIIa deficiency. Factor XIIIa catalyzes the formation of covalent cross links between the α and γ chains of fibrin clot. None of other screening test such as PT, APPT, TT detect factor XIIIa deficiency.⁹ Due to umbilical cord bleeding and abnormal clot solubility test we done factor XIIIa

assay which showed normal results. Hypofibrinogenemia is indicated by a proportional decrease of functional and immunoreactive fibrinogen. Dysfibrinogenemia is indicated by a discrepancy between functional and immunoreactive fibrinogen. Due to financial constrains above tests were not done. Fibrinogen disorders are the rare bleeding disorders account for 7% of rare bleeding disorders according to world federation of hemophilia annual survey.⁹ The cause of decreased synthesis of fibrinogen could be either homozygous deficiency (afibrinogenemia) or heterozygous (hypofibrinogenemia) due to mutations in 4q26-q28 genes.¹² Clinically hypofibrinogenemia divided into three types: (A) Mild, with levels between 1 and 1.5 g/l, which are usually asymptomatic (B) Moderate, with levels between 0.5 and 0.9 g/l and (C) Sever, with levels <0.5 g/l. moderate and severe types associated with bleeding manifestations.¹³

Plasma-derived FIB concentrates is the treatment of choice.¹⁴ The hemostatic level of fibrinogen is >60 mg/dL. In absence or unavailability of fibrinogen concentrate treatment with FFP or cryoprecipitate is also effective. Because the half-life of fibrinogen is 3-5 days, frequent infusions are usually not necessary. Each bag of cryoprecipitate contains 100-150 mg of fibrinogen. Bleeding is controlled by initially achieving plasma levels of 80 to 100 mg/dl followed by maintenance level >50 to 60 mg/dl until the bleeding subsides. These patients are peculiar susceptibility to spontaneous thrombosis and splenic rupture.^{15,16}

CONCLUSION

In conclusion PT, APTT are not good screening tests in hypofibrinogenemia. At peripheral hospital we need to do simple tests BT, CT for better approach. Levels of coagulation factors will vary since birth to childhood. Although less spontaneous bleeding has been reported in hypofibrinogenemia, should take necessary steps for prevention of bleeding like regular check-ups, care at immunization, avoiding sports, prophylaxis before surgery and dental care etc. We need to council the female child about complications like menorrhagia.

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