



A RARE CASE OF HYPOFIBRINOGENEMIA

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ABSTRACT

Afibrinogenemia is a rare bleeding disorder with a estimated prevalence of 1 in 10,00,000.^[1,2] It is a autosomal recessive disorder resulting from mutation of any of the 3 genes that encodes the 3 polypeptide chains of the fibrinogen and are located on the long arm of chromosome 4.^[3] Afibrinogenemia is often diagnosed at birth following prolonged umbilical cord bleeding and is characterized by spontaneous bleeding in all tissues, while hypofibrinogenemic patients are more often asymptomatic.^[4] Here by we present a case of Hypofibrinogenemia in a 2 year old female child who had repeated episodes of bleeding following a minor trauma to the oral cavity.

KEYWORDS: Afibrinogenemia, Hypofibrinogenemia.

CASE REPORT

Our case was a 2 year old female child, born of a third degree consanguineous marriage was admitted with complaints of repeated episodes of bleeding from oral cavity following a minor trauma. The child had history of prolonged bleeding from the umbilical cord even at 2 weeks of age. On examination child was pale with no petechiae or echymoses.

Investigations:

Hb:12.4gm%, WBC: 8300/cmm(N:35%, L:55%, M:5%,E:5%, B:0) , platelets 3,35,000/cmm.
PT:>600secs(control:12.9s),
APTT:>600secs(control:27s),
TT:>600secs(control:13.7s), No Clotting was seen after 30 minutes.

Plasma Fibrinogen levels: 50mg/dl(N: 200-400mg/dl).

A diagnosis of hypofibrinogenemia was made and the parents were counselled about avoiding aspirin, intramuscular injections and contact sports. Bleeding episodes where treated with cryoprecipitates.

DISCUSSION

Hereditary fibrinogen abnormalities comprise two classes of plasma fibrinogen defects: Type I, afibrinogenemia or hypofibrinogenemia, which has

absent or low plasma fibrinogen antigen levels (quantitative fibrinogen deficiencies), and Type II, dysfibrinogenemia or hypodysfibrinogenemia, which shows normal or reduced antigen levels associated with disproportionately low functional activity (qualitative fibrinogen deficiencies).^[5,6] Fibrinogen is a glycoprotein and is present at concentration of 200 to 400 mg/dl with half-life of 4 days.^[7] Afibrinogenemia and hypofibrinogenemia are characterised by fibrinogen values below 0.2 g/L and between 0.2 g/L and 0.8 g/L respectively. Afibrinogenemia is often diagnosed at birth following prolonged umbilical cord bleeding and is characterized by spontaneous bleeding in all tissues, while hypofibrinogenemic patients are more often asymptomatic. Two large case series, one from Iran.^[8] and the other from Israel.^[9] describe umbilical bleeding and mucosal haemorrhage as the most common bleeding problems. Musculoskeletal bleeding was not infrequent, and cerebral bleeding was reported. There is some evidence of impaired wound healing. Bleeding is less severe in hypofibrinogenemia but may occur following invasive procedures. Spontaneous spleen ruptures, painful bone cysts, cardiovascular events, and intrahepatic inclusions can complicate the clinical course of patients with quantitative fibrinogen disorders.^[4]

Acquired causes of hypofibrinogenemia and dysfibrinogenemia need to be ruled out. The most

common cause of acquired dysfibrinogenemia is advanced liver disease.^[10] Acquired hypofibrinogenemia can also occur with disseminated intravascular coagulation, and L-asparaginase and valproate therapy.^[11,12] The biological diagnosis is based on a standard haemostasis assessment. All the coagulation tests that depend on the formation of fibrin as the end point are affected; although in dysfibrinogenemia the specificity and sensitivity of routine test depend on reagent and techniques. A fibrinogen antigen-to-clottable fibrinogen ratio may help to distinguish dysfibrinogenemia (high ratio) from hypofibrinogenemia (ratio close to 1).^[13] A genetic exploration permits to confirm the diagnosis and may enhance the prediction of the patient's phenotype. Homozygous or composite heterozygous null mutations are most often responsible for afibrinogenemia while hypofibrinogenemic patients are mainly heterozygous carrier of an afibrinogenemic allele.^[14] The correlation between phenotype and genotype has been identified in some fibrinogen variants, including six mutations clustered in exons 8 and 9 of the FGG leading to hypofibrinogenemia with hepatic inclusions of abnormal fibrinogen aggregates as well as a few mutations associated with an increase risk of thrombotic events. A familial screening and additional functional assays should be carried out when possible.

Fibrinogen replacement therapy (FRT) is generally effective in treating bleeding episodes in congenital afibrinogenemia and hypo/hypodysfibrinogenemia. Options for replacement include plasma-derived fibrinogen concentrate (used in Europe and the U.S.), cryoprecipitate, and FFP.^[15,16] All products utilized for fibrinogen replacement are associated with a risk of development of antibodies and thromboembolic events. Topical fibrin glue or antifibrinolytic agents may be advocated for superficial bleeding events. Children have more rapid plasma fibrinogen clearance and may require higher and more frequent dosing for surgery and major bleeding. The therapeutic goal is to achieve a plasma fibrinogen activity level of 100-150 mg dL⁻¹ prior to surgery that is maintained until hemostasis is achieved and wound healing is complete.^[17]

Fibrinogen dosage calculation.^[18]

Dose (g) = desired increment in g/L x plasma volume x weight (kg)

Plasma volume = 0.07 × (1 - hematocrit)

Patient must be advised never to take aspirin, Prevent dental problems and gingivitis, to contact treating doctor in case of surgery or a tooth extraction in order to plan adequate preventive treatment, always wear a Medic-Alert type bracelet or a chain explaining the coagulation problem, to wear protective equipment and to avoid contact sports such as boxing, soccer and hockey.

REFERENCES

1. Acharya SS, Coughlin A, Dimichile DM. Rare Bleeding Disorder Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. *J Thromb Haemost.* 2004 Feb; 2(2): 248-56.
2. Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders. *Blood.* 2004; 104(5): 1243-1252.
3. Konstantinos, Tzimalos, Sofia Vakalopoulou, Vassilios Perifanis, and Vassilia Garipidou. *Vasc Health Risk Manag.* 2009; 5: 843-848.
4. Casini A, de Moerloose P, Neerman-Arbez M. Clinical Features and Management of Congenital Fibrinogen Deficiencies. *Semin Thromb Hemost.* 2016 Jun; 42(4): 366-74.
5. Lebreton A, Casini A. Diagnosis of congenital fibrinogen disorders. *Ann Biol Clin (Paris).* 2016 Aug 1; 74(4): 405-12.
6. de Moerloose P, Casini A, Neerman-Arbez M. Congenital fibrinogen disorders: an update. *Semin Thromb Hemost.* 2013 Sep; 39(6): 585-95.
7. Collen D, Tytgat GN, Claeys H, Piessens R. Metabolism and distribution of fibrinogen. I. Fibrinogen turnover in physiological conditions in humans. *Br J Haematol.* 1972; 22: 681-700.
8. Lak M, Keihani M, Elahi F, Peyvandi F, Mannucci PM. Bleeding and thrombosis in 55 patients with inherited afibrinogenemia. *Br J Haematol* 1999; 107: 204-6.
9. Fried K, Kaufman S. Congenital afibrinogenemia in 10 offspring of uncle-niece marriages. *Clin Genet* 1980; 17: 223-7.
10. Palascak JE, Martinez J. Dysfibrinogenemia associated with liver disease. *J Clin Invest* 1977; 60: 89-95.
11. Gralnick HR, Henderson E. Hypofibrinogenemia and coagulation factor deficiencies with L-asparaginase treatment. *Cancer*, 1971; 27: 1313-20.
12. Hauser E, Seidl R, Freilinger M, Male C, Herkner K. Hematologic manifestations and impaired liver synthetic function during valproate monotherapy. *Brain & Development*, 1996; 18: 105-9.
13. Cunningham MT, Brandt JT, Laposata M, Olson JD. Laboratory diagnosis of dysfibrinogenemia. *Arch Pathol Lab Med.* 2002; 126: 499-505.
14. Lebreton A, Casini A. Diagnosis of congenital fibrinogen disorders. *Ann Biol Clin (Paris).* 2016 Aug 1; 74(4): 405-12.
15. Bornikova L, Peyvandi F, Allen G, Bernstein J, Manco-Johnson MJ. Fibrinogen replacement therapy for congenital fibrinogen deficiency. *J Thromb Haemost* 2011; 9: 1687-704.
16. Peyvandi F. Results of an international, multicentre pharmacokinetic trial in congenital fibrinogen deficiency. *Thromb Res* 2009; 124 Suppl 2: S9-11.
17. Manco-Johnson MJ, Dimichele D, Castaman G, Fremann S, Knaub S, Kalina U. Pharmacokinetics and safety of fibrinogen concentrate. *J Thromb Haemost.* 2009 Dec; 7(12): 2064-9.

18. Acharya SS, Dimichele DM. Rare inherited disorders of fibrinogen. *Haemophilia*. 2008 Nov; 14(6): 1151-8.