Case Report

Afibrinogenemia

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Abstract

Afibrinogenemia is a rare bleeding disorder with an estimated prevalence of 1: 10,00,000.[1,2] It is an autosomal recessive disease resulting from mutations in any of the 3 genes that encodes the 3 polypeptide chains of fibrinogen and are located on the long arm of chromosome 4.[3] Spontaneous bleeding, bleeding after minor trauma, and excessive bleeding during interventional procedures are the principal manifestations.[2,4] Here we have reviewed the process of diagnosing a case of such rare disorder in Apollo Hospitals Dhaka. We have also highlighted the treatment and management plan of such a case.

Introduction: Afibrinogenemia is a very rare inherited disorder in which factor 1 or fibrinogen deficiency occur.[5] Afibrinogenemia is an autosomal recessive disease and most of the patients are commonly descendents of consanguineous marriage.[1,2,4] It was first discovered in 1920 by two German physicians, Fritz Rabe and Eugene Salomon. People affected by this disorder and those close to them have very little written information about it.[5] This literature therefore seeks to provide information for people trying to cope with this health problem. Here we present a case with afibrinogenemia, the process of diagnosis and explain the causes of the disorder and currently available treatments.

Case summary: Muna, a 3 years old girl, weighing 11.5 kg having 0.93 meter height, only issue of a 1st degree consanguineous parents, was admitted in Paediatric department, Apollo Hospitals Dhaka with the complaints of multiple bruises and echymoses all over the body. She had h/o same type of bleeding spots on limbs during crawling or after falling on ground while walking or running. Her mother stated that there was bloody discharge from the umbilical stump even at 2 weeks of her age. Her milestones of development were slightly delayed. She had no h/o hospital admission for this illness and there was no h/o such type of illness in her family.

Physical examinations on OPD visit revealed temperature 98.4*F, H.R-130 b/m, R.R-20/m. She was conscious, cooperative, having mild pallor, multiple bruises and echymoses on lower limbs, also a few on upper limbs and trunk, sparing face (Fig 1-3).

Relevant investigations were done as stated below:

HB%: 11.4gm/dl, PCV: 0.33L/L, MCV: 78.0fl, MCH: 27.0pg, MCHC: 34.0%, Platelets: 362 10^g/L, RBC: 4.3 million /c mm, TLC: 10.7 10^g/L, N: 27%, L: 62%, E: 09%, B: 00%, M: 02%, BT: 7 min, CT: Clotting was not seen within 30 minutes, PT: >118 sec (contr:12-14sec), INR: >12, APTT: >180sec (contr:32-38sec), TT: >60 sec(contr:17.0sec), Urea solubility test (2% acetic acid): result unstable.

Investigation reports with prolonged CT, PT, APTT & TT suggests clotting disorder. This picture could be found in liver disease, fibrinogen deficiency and inhibition of fibrin polymerization or Hyperfibrinolysis.[6] Serum fibrinogen level of this girl was less than 15 mg /dl (ref:200-400mg/dl). Liver disease was also excluded by normal liver function tests: total S. Bilirubin 0.5 mg/dl (normal range- 0.5-1 mg/dl), S. SGPT: 27 IU/L (norm: 5-40 IU/L), Alkaline Phosphatase; 229 IU/L (32-385 IU/L).Total protein and A/G ratio were also within normal limit. Hence, this is a case of fibrinogen deficiency disorder, Afibrinogenemia.

Counseling to the parents was done about the disease, treatment and protection of the baby.

Discussion: Fibrinogen/factor I, a plasma protein produced by the liver plays an important role in blood coagulation, missing or functional problems of which results in hemorrhage or thrombosis.[5] These fibrinogen disorders can present as afibrinogenemia or hypofibrinogenemia (quantitative defects) or dysfibrinogenemia (qualitative defects).[7] The normal volume of fibrinogen in the blood is from 2 to 4 g/l.[5]

Afibrinogenemia is a very rare inherited bleeding disorder that affect both male and female of all races and ethnic origin.[5] The first clinical report of congenital of afibrinogenemia dates back to 1920 when a 9 year old boy suffering from recurrent bleeding episodes since birth and lacking of fibrinogen in blood was described and shown subsequently to be autosomal recessive in inheritance with variable penetrance.[6,8]

The estimated prevalence of afibrinogenemia which is most severe form of the disorder is around 1 in 10 lacs[9] and recent registries from Italy, Iran and North America have greatly improved understanding of the clinical spectrum of presentation.[6,10] In fact, a seven fold higher incidence of fibrinogen disorders was observed in the Iranian Registry (where consanguinity is high) for rare bleeding disorders in comparison with similar registries in Italy and United Kingdom.[8]

In congenital afibrinogenemia (fibrinogen level <0.2 g/l), bleeding can vary, from slight to severe.[5] Bleeding can start in the neonatal period with 85% presenting with umbilical cord bleeding[10] or bleeding into the skin, gastrointestinal tract, genitourinary tract or central nervous system bleeding

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(5%).[6,8] Musculoskeletal bleeding (including hemarthroses) occurs in 54% of the patients.[8,4] In afibrinogenemia unusual manifestations such as spontaneous rupture of the spleen and presence of bone cysts are also observed.[11] In females menorrhagia (7%) have been noted.[11,12] Further, impaired wound healing and wound dehiscence post surgery have been reported because of the non tensile clot and inadequate deposition of healing proteins delaying wound healing.[7]

It is strongly recommended that people who suffer from afibrinogenemia learn to recognize the signs and symptoms of bleeding that could threaten their lives or the integrity of a limb, so that they can react adequately and in a reasonable time.[5] Bleeding that affects the head, neck, chest or abdomen can be life-threatening and may require immediate medical attention. This kind of bleeding can occur either following an injury or spontaneously.[5] Intra cranial hemorrhage is very serious, and may be manifested as headache, visual problem, nausea, vomiting, change of personality, somnolence, loss of balance, loss of fine motor skills, fainting or convulsion. Intrathoracic bleeding may present with chest pain, breathing difficulty, cough or bloody sputum or swallowing difficulty. Intra abdominal hemorrhage causes pain in abdomen or low back pain or blood in urine or stool.[5] If one of these symptoms occurs, immediate consultation with a physician is necessary.

There are other kinds of bleeding that are not necessarily life-threatening, but for which treatment is necessary.[5] These are soft tissue bleeding, bleeding in the joints manifested by reduced joint mobility, or swelling or heat in the joint with or without bruising.[6]

Replacement therapy is the mainstay of treatment of bleeding episodes in patients with afibrinogenemia and includes plasma-derived fibrinogen concentrate, cryoprecipitate and fresh frozen plasma.[13] The aim of the treatment is to increase the fibrinogen level to 1g/L when there is minor bleeding, and 2 g/L for serious bleeding or for surgery.[5] The girl in our hospital was treated with fresh frozen plasma due to lack of availability of other options. At present, the most frequently used treatment abroad is fibrinogen concentrate. The concentrate is obtained from human plasma and contains fibrinogen only.[6] The quantity of fibrinogen required can be calculated as follows:

Dose (g) = Desired increment (g/l) × plasma volume × patient weight (kg).[13]

Here, plasma volume = 0.07 × (1- hematocrit).

There are five fibrinogen concentrates currently available: Hemocomplettan P (CSL Behring, Marburg, Germany), Clottagen and FIBRINOGENE T1 (LFB, Les Ullis, France), Fibrinogen HT (Benesis,Osaka, Japan) and FibroRAAS (Shangai RAAS, Shangai,Chaina).[14,15]

Prevention is very important for this disease. The patient was advised never to take aspirin, and to prevent dental problem she needs to visit dentist every six months.[5] The patient should always contact with hematologist if she needs surgery or a tooth extraction in order to plan adequate preventive treatment.[5] She also advised to carry a card explaining her coagulation problem. Contact sports were also asked to avoid due to the significant risk of bleeding.[5] She is also recommended to receive vaccine against hepatitis A and B by fine needle.

Conclusion: Even though afibrinogenemia is a rare disorder, it might acquire greater importance in future when this disorder might be more prevalent due to increasing consanguineous marriages. Patients with afibrinogenemia should be referred to and registered with a center of bleeding disorders guided by hematologist. The development of new tests to identify higher risk patients and safer replacement therapy will improve the management of these cases in future.

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