

A Case Report of Congenital Afibrinogenemia

Aysen Turedi Yıldırım¹, Gokmen Bilgili², Ozlem Buga³, Ozen Tekin³, Huseyin Gulen¹

Abstract

Congenital afibrinogenemia is a rare bleeding disorder. It may be manifested as umbilical, mucosal, intramuscular, intraarticular, or life-threatening intracranial bleeding. A third-day-old infant was admitted for umbilical cord bleeding, and was found to have a prolonged prothrombin time [PT], and activated partial thromboplastin time [aPTT], and a very low fibrinogen level. He was diagnosed as congenital afibrinogenemia, and reported for the rarity of disease, and discussion of novel therapeutic approaches

Keywords: Congenital afibrinogenemia, umbilical cord bleeding, fibrinogen concentrate

Introduction

Afibrinogenemia is a very rare bleeding disorder, characterized as a functional disorder of plasma fibrinogen, or its complete absence. Fibrinogen plays a key role in the last step of the coagulation pathway. It is the basic molecule required for the formation of insoluble fibrin clot. Fibrinogen also acts like a bridge between the trombocytes for the formation of thrombocyte clot [1]. Afibrinogenemia is inherited as an autosomal recessive trait, and estimated to have an incidence of 1-2 in a million in the Western world. Its incidence is higher in the Middle East, and in the southern of India, where parental consanguinity is frequent [2]. Uncontrolled umbilical bleeding is observed in 85% of patients, which is a bleeding profile not observed in hemophilia. Ecchymosis, Intra-articular hemorrhage, posttraumatic, or postsurgical bleeding are similar manifestations, as seen in hemophilia patients [3]

Case

A male infant born at 37th gestational week to a 22-year-old, healthy, G1P0 woman was admitted to our hospital for jaundice and umbilical bleeding. He had ongoing bleeding from the injected site of vitamin K, administered in the hospital of referral. Physical examination also revealed jaundice, but was otherwise unremarkable. Body weight, length, and head circumference were within the normal percentiles for his age. His complete blood count was as follows: hemoglobin: 13.8 g/dl, leucocyte count: 6830/mm³, trombocyte count: 230,000/mm³; and the peripheral blood smear revealed abundant and clustered trombocytes. The total bilirubin and alanine serum transferase levels were elevated (17.3 mg/dl, and 143 U/L, respectively), and the biochemical analysis was otherwise normal. The coagulation profile following vitamin K administration revealed a prolonged PT (>120 seconds), and aPTT (>160 second), and a diminished fibrinogen (<50 mg/dl) level. Diagnosed as congenital afibrinogenemia, fresh frozen plasma (FFP) was commenced (15 ml/kg bid),

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¹Celal Bayar University Department of Pediatric Hematology, Manisa-Turkey

²Celal Bayar University Department of Neonatology, Manisa-Turkey

³Celal Bayar University Department of Pediatrics, Manisa-Turkey

*Corresponding Author: Gokmen Bilgili gokmenbilgili@yahoo.com

and fibrinogen levels were kept well above 100 mg/dl, controlling umbilical bleeding in the first day of treatment. FFP infusions were withheld on the 2nd day; however, on the 7th day following FFP infusions, fibrinogen levels were unmeasurably low, whereas PT and aPTT values were unmeasurably high. The infant was clinically stable, without any signs of bleeding, and was put on a prophylaxis of fibrinogen concentrate (100 mg/kg/dose, once 2 weeks), and followed up in the outpatient clinic. Upon absence of any re-bleeding episodes at the 3rd month of the follow-up, the prophylaxis was prolonged to once a month. No complications were observed regarding prophylaxis.

Discussion

Most common signs of afibrinogenemia include umbilical cord bleeding, and bleeding from mucosal surfaces, particularly menorrhagia, epistaxis, and oral mucosal hemorrhage. Musculoskeletal bleeding is reserved for the half of the patients, whereas gastrointestinal and urinary system bleeding account for the less. Intracranial hemorrhage is rare [4]. Bleeding tendency, even among those carrying the same mutation, is quite variable. Yearly hemorrhagic episodes do occur multiply in some, and occasionally in other patients [5]. Reasonable explanations include the presence of yet-unidentified modified genes, or coexistence of a thrombophilic disorder [6]. Our patient was admitted for umbilical cord bleeding.

Fibrinogen is encoded in the 4q28-q31 by 3 genes, occupying a wide zone of 50 kb, namely the fibrinogen alpha (FGA), beta (FGB), and gamma (FGG). More than 80 mutations in fibrinogen encoding genes have been identified in afibrinogenic, or hypofibrinogenic patients, most (70%) being missense mutations. Various specific mutations are relevant to distinct forms of congenital fibrinogen deficiency. Most of the genes involved are those of the FGA

gene. Two specific mutations of this gene (FGA IVS4+1G>T c.510+1G>T, FGA 11-kb deletion) are more commonly observed in Europeans [7, 8]. The exact diagnosis can be done by identifying the molecular defect. Afibrinogenemia is characterized by the complete absence, or diminished levels of immunoreactive fibrinogen measured by antigenic or functional assays. Coagulation tests, including PT, aPTT, thrombin time, and reptilase time are exceedingly prolonged, and fibrinogen levels cannot be determined by functional, or immunoreactive assays [9]. Gene mutations could not be explored in our patient, however, a diagnosis of congenital afibrinogenemia could be made by showing profoundly prolonged PT, aPTT, and an extremely low fibrinogen level.

Fibrinogen concentrates are available as replacement therapy in afibrinogenemic patients. Virus inactivation, small-volume infusions, and low risk of allergic reaction are their major advantages over other replacement therapies [10]. Cryoprecipitate and FFP should be infused only on an emergency basis, when fibrinogen concentrates are unavailable [11]. Unavailability of fibrinogen concentrate on the day of admission in our patient led us to infuse FFP, with resultant control of bleeding without treatment complications. Thrombotic complications may be observed in afibrinogenemic patients during replacement therapy, such as ischemic feet lesions, ischemic stroke, renal or ovarian vein thrombosis, deep vein thrombosis, and pulmonary emboli [12, 13, 14, and 15]. Thrombophilic disorders, such as protein C deficiency may accompany afibrinogenemia, wherein thrombotic tendency is increased by replacement therapy [15]. Primary prophylaxis with fibrinogen concentrates, or cryoprecipitate should be considered in early ages for bleeding prevention [16]. Secondary prophylaxis may be commenced to prevent re-bleeding, particularly following life-threatening hemorrhages, which commonly consist of weekly infusions. Infusions once

two weeks, or a month may be applied as well [17, 18]. Our patient was on primary prophylaxis with fibrinogen concentrates once two weeks, prolonged to once a month upon lack of re-bleeding episodes.

As to sum up, afibrinogenemia is a very rare disorder, manifesting most frequently as umbilical cord bleeding during the neonatal period. The most important laboratory findings include prolonged PT, aPTT, and low fibrinogen levels. Fibrinogen levels should be determined in patients with bleeding on admission, when PT and aPTT are found to be prolonged. For the prevention of bleeding episodes, prophylaxis with fibrinogen concentrates may be administered.

Conflict of Interest

The authors declared that they had no conflicts of interest.

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