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CASE REPORT

# Management of Congenital Afibrinogenemia: Report of Two Cases

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## Abstract

**Background:** Fibrinogen (Factor I) is an essential factor in the coagulation cascade. The activation of prothrombin to thrombin by Factor X is followed by the activation of fibrinogen. In turn, thrombin converts fibrinogen to fibrin, which is the end target of both extrinsic and intrinsic pathways. A deficiency in fibrinogen results in the tendency to bleed [1].

Congenital afibrinogenemia is a rare bleeding disorder. Hemorrhagic manifestations vary from minimal to catastrophic bleed. It may include fatal umbilical cord hemorrhage as the first disease manifestation. In later life, the disorder may be associated with bleeding from mucosal surfaces including epistaxis, menorrhagia, gastrointestinal bleeding, hemorrhage into muscles and joints and intracranial bleeding, spontaneous abortions, and/or spontaneous splenic rupture. Thrombotic manifestations can also occur from impaired thrombin inhibition. Due to its rarity and the lack of clinical practice guidelines in the management of congenital afibrinogenemia, this case report can be a potential starting point to provide a high quality of evidence to manage such patients.

**Case report:** We describe two cases, who are sisters, of congenital afibrinogenemia. Case A is a 14-years-old girl while her sister (case B) is now 2-years-old and 9-months-old. Both of them were diagnosed with congenital afibrinogenemia. They both presented with bleeding from several orifices and showed a marvelous response to weekly infusions of fibrinogen concentrate as a preventive program with no breakthrough bleeding.

**Conclusion:** A weekly infused Human Fibrinogen Concentrate can be a potential target therapy for patients with congenital afibrinogenemia who failed to respond to conventional therapy with cryoprecipitate. Further placebo-controlled studies are required to generalize this conclusion.

## Keywords

Congenital afibrinogenemia, Fibrinogen concentrate, Hematology, Thrombosis

## Background

Fibrinogen (Factor I) is a blood plasma glycoprotein of 340 kDa size that is synthesized by the liver. Its structure is composed of three polypeptide chains, i.e., alpha, beta, and gamma chains that interact with each other to form the hexametric structure [1]. A separate gene encodes each polypeptide; α polypeptide is encoded by FGA, a β polypeptide is encoded by FGB, γ polypeptide is encoded by FGG [2]. Fibrinogen is essential for hemostasis [3].

The activation of prothrombin to thrombin by Factor X results in the conversion of fibrinogen to fibrin, which is the end target of both extrinsic and intrinsic pathways. Deficiency of fibrinogen results in increased bleeding or functional problems, which may result in further hemorrhage or thrombosis. These disorders can be quantitative defects such as afibrinogenemia or hypofibrinogenemia, or qualitative defects such as dysfibrinogenemia [4].

Congenital afibrinogenemia is a rare bleeding disorder. As mentioned earlier, fibrinogen is the precursor of fibrin, which is the major protein of blood clots [5]. There are more than 40 mutations located in fibrinogen genes, FGA, FGB, and FGG that can cause congenital afibrinogenemia. The vast majority of mutations have been reported in FGA gene [6]. The normal level of fibrinogen in the blood is from 2 to 4 g/L. A few case reports have revealed that thrombosis is associated with afibrinogenemia [1]. In congenital afibrinogenemia, the bleeding varies in severity, from mild to life-threatening. Bleeding affecting the head, neck, and abdomen, which usually occur following injury or can happen

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**Table 1:** The given and normal parameters of case A.

| Parameters | Patient's value | Reference range |
|---|---|---|
| CBC | 11.9 (g/dL) | 11.5-15 (g/dL) |
| Platelets | 560 (× 103/μL) | 150-450 (× $10^3$/μL) |
| MCV | 75 (fl) | 70-86 (fl) |
| MCH | 24.7 (pg) | 23-31 (pg) |
| MCHC | 33.4 (%) | 30-36 (%) |
| Hematocrit | 32.9 (%) | 42.0-60 (%) |
| RBC count | 4.45 (× $10^6$/μL) | 3.90-5.30 (× $10^6$/μL) |
| WBC | 9.5 (× $10^3$/μL) | 5.5-15.5 (× $10^3$/μL) |
| Total bilirubin | 3 mg/dL | < 1.0 mg/dL |
| Alkaline phosphatase | 23 U/L | 96 - 297 U/L |
| Albumin | 4.3 g/dL | 3.8 - 5.4 g/dL |
| Anion gap | 16 | 8 - 12 |
| $Co_2$ | 22 mmHg | 35 - 60 mmHg |
| $K^+$ | 4.2 mmol/L | 3.5 - 5.8 mmol/L |
| $Na^+$ | 142 mEq/L | 135 - 145 mEq/L |
| Creatinie | 42 (mol/L) | 17.7 - 61.9 (mol/L) |
| Erythrocyte sedimentation rate | 1 mm/hr | 3 - 13 mm/hr |
| Blood film result | Platelets appear high. With target cell, anisocytosis<br>No promyelocyte, myelocyte, metamyelocyte band, Basophil | Not Applicable |
| RDW | 16.7% | 11.5 - 15% |
| Platelets function analysis | 133 with no aggregation | 62 - 100 seconds |
| von Willebrand factor | 115.5% | 50 - 150% |
| Fibrinogen | 0 | 150 - 400 mg/dL |

spontaneously, should be given immediate treatment. Intracranial hemorrhage may manifest as a headache, visual problems, fainting, convulsion, or loss of fine motor skills.

Intrathoracic bleeding can present as chest pain, difficulty in breathing, coughing or having hemoptysis. Intraabdominal hemorrhage can cause pain in the abdomen or the lower back and can also cause nausea, vomiting, and blood in urine or stool. There are other kinds of bleeding that not necessarily life threatening but for which treatment is necessary such as mild soft tissue bleeding and mild bleeding in the joints [1,7]. Afibrinogenemia, which is the rarest and most severe form of fibrinogen, is diagnosed when the fibrinogen level falls below < 0.2 g /L. Hypofibrinogenemia, usually milder than afibrinogenemia, is diagnosed when the fibrinogen level is between 0.2 - 0.8 g/l. Dysfibrinogenemia, a functional disorder of fibrinogen, is usually diagnosed using Thrombin Time Test; the Prolongation of Thrombin Time (Thrombin Clotting Time) in the absence of any anticoagulation and normal levels of fibrinogen strongly suggest dysfibrinogenemia.

## Case Report

We describe two cases of congenital afibrinogenemia as case A and case B as follows:

### Case A

Case A is a female, who is now 14-years-old, with congenital afibrinogenemia. In March 2006, she first presented with fever and right leg swelling for 2 days at the age of 4 years. Her examination revealed normal findings with no obvious pallor or bleed except for right leg swelling (See Table 1 for investigations). After establishing a diagnosis of congenital afibrinogenemia provided by the absence of circulating fibrinogen, a plan of management was initiated in the form of five units of cryoprecipitate to be administrated over 30 minutes. No allergic reaction was noted, and she had stable vital signs. She was adherent to this regimen for seven years. She subsequently developed an allergic reaction to cryoprecipitate with episodic attacks (variable frequency and seriousness) of bleeding later on. A major life-threatening intracranial bleeding was noted that necessitated a change in the management plan. On February 2013, the patient was started on the preventive program after a catastrophic intracranial bleed. A 70 mg/kg of fibrinogen concentrate (Haemocomplettan-P from CSL Behring) was used as a slow IV infusion, on a weekly basis with serial follow-up until July 2016. No evidence of recurrent hospitalization or breakthrough bleeding has been since noted.

### Case B

Case B is a female aged 2 years and 9 months with congenital afibrinogenemia. She was born full term with unremarkable antenatal history and a birth weight of around 3.5 kg. She was subsequently discharged along with her mother in a good status after 24 hours.

At the age of 6 days, she presented to pediatric emergency room with complaints of bleeding from umbilicus noticed by her mother one day prior to admission. The bleeding started suddenly with a spot on the diaper, which increased progressively until the whole diaper was soaked with blood. No pus or other discharges were noted in the umbilicus. No history of bleeding from oth-

er orifices in the mouth (gum) or in the urethra (urine) or per rectum (stools). There were no other associated symptoms; specifically, no fever, skin rash, or history of trauma was observed. Family history showed that parents are first degree relatives, indicating a positive consanguinity. She has an older sister who was diagnosed with severe congenital afibrinogenemia (case A).

Physical examination revealed stable vital signs with no tachycardia, hypotension, or tachypnea. Umbilicus exam showed red and erythematous umbilicus. There was blood oozing from the umbilicus. Blood work at that time showed hemoglobin level of 14.1 g/dL and platelet count was 387 × 103/µL. Fibrinogen was 0. Prothrombin time, international normalized ratio, and partial thromboplastin time were all prolonged. She was admitted to the pediatric medical ward when she was transferred to the pediatric intensive care unit, where she received 1 unit of cryoprecipitate with repeated doses of Fresh Frozen Plasma (FFP). After one dose of FFP, her fibrinogen level rose to 32 mg/dl. Bleeding stopped after several doses of FFP. One day after, she had a head ultrasound, which showed no evidence of intracranial bleeding. After stabilizing the patient, she was booked for hematology and thrombosis clinic. She experienced multiple episodes of bleedings and was seen by hematology service. In light of her recurrent bleeding and admission, a decision was made to start her on primary prevention program, which consists of weekly infusions of fibrinogen concentrates as her older sister. An adjusted dose of her weight is 0.5 g/L weekly (approximately 70 mg/kg IV). Until July 2016, no breakthrough bleeding has been noted with an excellent adherence to prevention program for both cases.

## Discussion

Congenital afibrinogenemia is an autosomal recessive condition that was described first in 1920 [7]. Since then, more than 150 cases have been reported in the literature. The genes involved in this disorder are located on chromosome 4 (q26- q28) and are associated with various types of mutations [7].

The mainstay treatment for fibrinogen disorder is human fibrinogen concentrate (HFC) [8]. Hemostasis can be maintained by replacing fibrinogen to a level of more than 0.8 g/L. If there is a minor bleeding, the aim is to increase fibrinogen up to 1 g/L; in case of serious bleeding or prior to surgery, the level of fibrinogen is increased up to 2 g/L [8]. There are five commercially available fibrinogens concentrates: Haemocomplettan® P (CSL Behring, Marburg, Germany), which was used in our cases, Clottagen® and FIBRINOGEN T1® (LFB, Les Ulis, France), Fibrinogen HT® (Genesis, Osaka, Japan) and FibroRAAS® (Shangai RAAS, Shangai, China) [8]. Cryoprecipitate or FFP can be an alternative in emergency settings when the fibrinogen concentrate is not available [8]. Cryoprecipitate has higher concentrations of fibrinogen, but methylene blue/visible light treatment of cryoprecipitate may reduce the fibrinogen level by 40% [9]. Each unit of cryoprecipitate contains 140 mg of Fibrinogen. Classically, virally-inactivated FFP is preferred over non-virally inactivated cryoprecipitate [9,10]. Compared to cryoprecipitate, HFC offers more benefits in terms of purity, accuracy of dosing, feasibility of administration, and improved safety [9].

The management of thrombosis in the background of congenital afibrinogenemia is a real challenge for physicians due to the bleeding tendency. Some experts recommend using a dual therapy that targets both the thrombosis and afibrinogenemia by introducing low-dose heparin with fibrinogen concentrate [11]. However, Haemocomplettan does have a half-life similar to the physiological fibrinogen in a normal individual that ranges from 2.5 to 5.2 days with an average of 3.4 days among patients who received fibrinogen concentrate. The recommended dosage to adequately replace fibrinogen level in the case of congenital afibrinogenemia is as follows:

Dose (g) = 0.7* desired increment (g/L) × (1 - Hematocrit)

*patient's weight in Kg [8].

Several preventive measures have been proposed to prevent the occurrence of catastrophic bleeding in patients with congenital afibrinogenemia [12]. A weekly infusion is a widely accepted regimen for treating hematologist, but monthly and every 2 weeks regimens have also been used [10]. Surprisingly, the frequency of bleeding among the group who enrolled in the preventive program is the same as the group who received the replacement therapy on-demand [12]. The desired therapeutic target is to maintain the level of fibrinogen above 0.5 g/L [13]. A prophylactic infusion is not recommended in naïve patients with no history of catastrophic bleeding due to the high risk of exposure to blood-borne diseases, allergic reactions, and thrombotic complications [13].

In our case, we have two patients, who are sisters, diagnosed with congenital afibrinogenemia. The older one is a 14-year-old with a history of intracranial hemorrhage. The younger one is aged 2 years and 9 months and was diagnosed with congenital afibrinogenemia after suffering from umbilical cord bleeding in the neonatal period. Both were treated initially with FFP and cryoprecipitate. Lately, and for the last 2 years, they have been treated symptomatically and prophylactically with plasma-derived fibrinogen concentrate (Haemocomplettan-P from CSL Behring). The dose for the older one is 70 mg/kg per dose once every week (1.5 g) while for the younger one is also 70 mg/kg/dose per week (0.5 g/L). Both of them responded well to the treatment. There was no documented breakthrough bleeding while on prophylaxis.

## Conclusion

Due to the high prevalence of consanguineous marriage in the Middle East and North Africa, high-quality evidence and clinical practice guidelines should be available to facilitate the clinician to take an evidence-based decision that ensures a better quality of care for patients with fibrinogenic disorders. Advances in diagnostic and preventive measures will improve the management of these patients in future.

## Conflict of Interest

The authors declare that there are no conflicts of interest.

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## Ethical Approval

The consent was obtained from the mother of both sisters to publish the two cases for educational purposes.

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