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Varied Clinical Manifestation of Congenital Afibrinogenemia: From Thrombosis to Intramedullary Hemorrhage - A Case Series of 7 Patients

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Abstract: ***Congenital afibrinogenemia is a rare autosomal recessive disorder characterized by complete absence of detectable fibrinogen in circulation. There are about 250 cases reported in the world literature. Afibrinogenemia and hypofibrinogenemia represent the homozygous and heterozygous states, respectively, for mutations affecting plasma fibrinogen concentration. Here we report 7 cases with varied clinical manifestations at presentation. In our case series, 3 patients presented with bleeding symptoms, one patient with bleeding as well as thrombosis and one with recurrent abortions.***

Keywords: afibrinogenemia, fibrinogen, thrombosis, bleeding, abortion

1. Introduction

Afibrinogenemia is a rare condition, most often with autosomal recessive inheritance in association with consanguinity. The estimated incidence is one per million in the general population. Bleeding manifestations vary from mild to severe. Umbilical cord bleeding is a common manifestation. Joint, mucosal and intracerebral bleeding, splenic rupture, or miscarriage can occur throughout life. [1]Paradoxical arterial and venous thrombosis may be a manifestation but it is rare. [2]

2. Case Presentation

Here we report 7 cases with varied clinical manifestations at presentation. All seven patients are females with age ranging from 1.5 years to 35 years at presentation. There was no family history of bleeding in these patients. History of 3rd-degree consanguinity was present in 2 cases.

The first patient presented at 1.5 years with excessive bleeding from venipuncture site and history of prolonged umbilical cord bleeding. She was evaluated for the same, at the time of a routine surgery for squint correction. On evaluation, she was found to have an undetectable level of fibrinogen with prolonged PT, APTT and Thrombin time. This patientwas managed conservatively and her parents were counselled about disease and precaution to be taken before any procedure or surgery.

The second patient had bleeding symptoms from the age of 1 year and was diagnosed to have afibrinogenemia. She presented to us at 10 years of age, with recurrent severe left lower limb pain, ecchymosis and easy bruisibility. On clinical examination, there was no swelling or tenderness in the limbs. Her X-ray and USG of thigh were normal. However, she continued to have intermittent severe pain. Thus, left thigh with knee joint magnetic resonance imaging was done. This showed the presence of a bleed in the intramedullary region of meta-diaphysis of left femur (Fig.1).After one year, she had severe pain in the left thigh with no abnormalities on clinical examination. Her Magnetic resonance imaging of left thigh showed multiple intramedullary cysts in left femur (Fig.2).

The third patient presented to us at 14 years, with puberty menorrhagia and severe anemia requiring blood transfusion. Her investigations revealed an absence of fibrinogen.

The fourth patient presented with hemoperitoneum with a hemorrhagic ovarian cyst at the age of 20. She was managed conservatively with cryoprecipitate infusion. The same patient at the age of 32 years came with abdominal pain and splenomegaly. Her Doppler studies revealed complete thrombosis of the portal and splenic veins, which were replaced by multiple collaterals forming a portal cavernoma (Fig.3).Work up for inherited and acquired thrombophilia was negative. DNA sequence analysis of the 3 fibrinogen genes revealed missense mutation in FGB gene.

The fifth patient presented with prolonged bleeding after a missed abortion at 6 weeks of gestation. She also gave the history of seven recurrent first trimester abortions. During her eighth pregnancy, she presented to KEM hospital. Initially, she had an incomplete abortion with prolonged PT, APTT >300 seconds, thrombin time and Fibrinogen level less than 50 mg/dl.Herplatelet count was 200× 10^9/L.

Shewas managed with cryoprecipitate and bleeding stopped. Work up for acquired and inherited thrombophilia showed only heterozygous MTHFR mutation. Her molecular studies showed homozygous deletion mutation in FGB gene.

The sixth patient, 11-year-old female, born of non-consanguineous marriage presented with swelling in the left gluteal region following trauma.She had history of recurrent episodes of epistaxis and prolonged bleeding following minor cuts from 3 years of age for which she was not evaluated. She was found to have left thigh hematoma. Her coagulation profile showed prolonged PT, APTT and low Fibrinogen (<50 mg/dl) and she was managed with Cryoprecipitate. Repeat coagulation profile on 3rd day of admission showed normalization of all parameter except Fibrinogen which was low (i.e. <50 mg/dl). On 6th day, her swelling increased in size and was not responded to repeated cryoprecipitate transfusion so inhibitor was suspected. Diagnosis of afibrinogenemia with inhibitor was made on mixing studies. Exons in FGA couldn't be amplified suggesting gross deletion on mutation analysis. The patient however died on day 13 of hospital admission due to severe gastro- intestinal and pulmonary hemorrhage.

Another patient presented with brain abscess at 11 months of age, posted for surgery found to have deranged coagulation parameter and diagnosed as afibrinogenemia.

Table 1: Investigations

Patient	1	2	3	4	5	6	7
PT (seconds)	>120	>300	>600	>600	>300	>120	>300
APTT(seconds)	>600	>300	>600	>600	>300	>120	>300
TT (seconds)	>600	>300	>600	>600	>100	>100	>300
Serum Fibrinogen(mg/dl)	Not detected	Not detected	<50	<50	Not detected	<50	Not detected
Platelet count($\times 10^9$/L)	560	240	281	200	380	1.5	2.1
Doppler study				Portal and splenic vein thrombosis			
Thrombophilia Work up				Negative	MTHFR heterozygous mutation		
Magnetic resonance imaging		Intramedullary Bleed in meta-diaphysis of femur					Brain abscess
Genetic study				Missense mutation in FGB gene	Deletion in FGB gene	Deletion in FGA gene	

PT- prothrombin time, APTT- activated partial thrombin time, TT- thrombin time, MTHFR- methyl tetrahydrofolate reductase

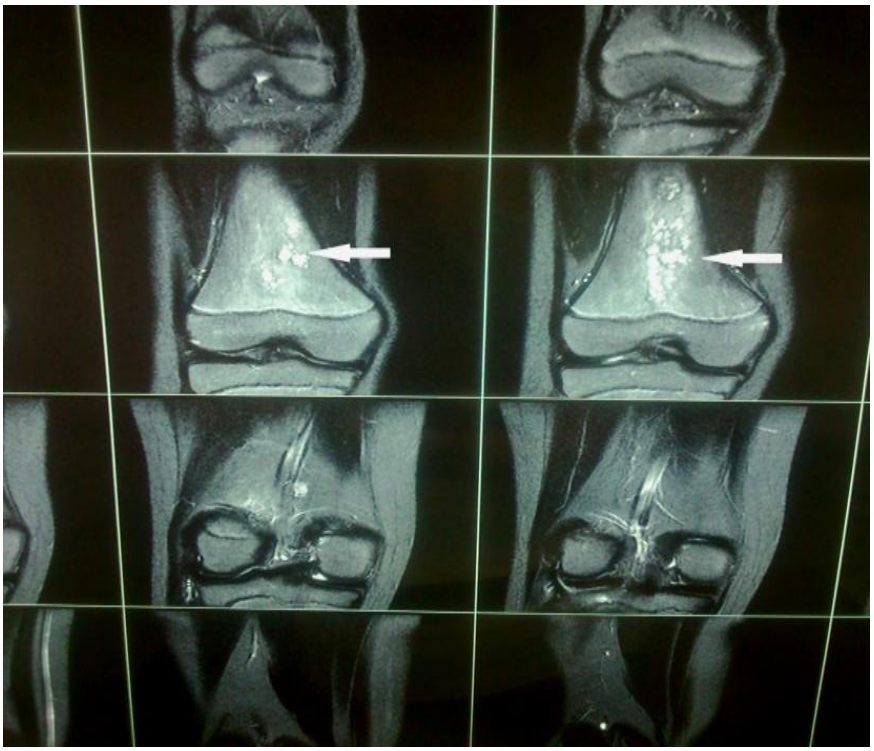

Figure 1: Magnetic resonance T2 -image of left thigh showing intramedullary bleed in meta-diaphysis of femur (arrow) intramedullary bleed

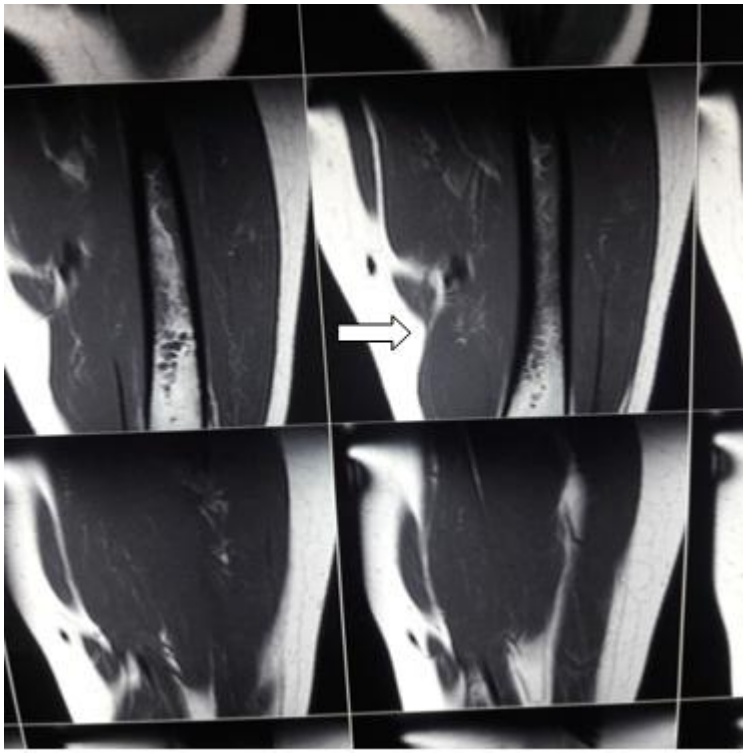

Figure 2: Magnetic resonance T1- image of left thigh showing intramedullary cysts in diaphysis of femur (arrow)

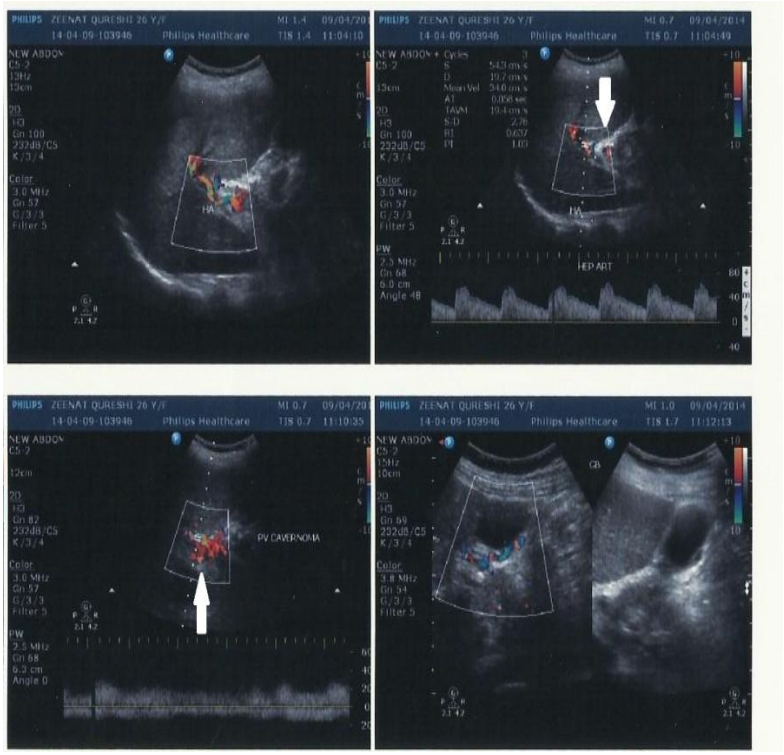

Figure 2: Colour Doppler of abdomen showing Portal and Splenic thrombosis (arrow)

3. Discussion

Congenital afibrinogenemia is a rare autosomal recessive disorder described for the first time in 1920.[4]It is characterized by unmeasurable or extremely low fibrinogen levels in plasma. Fibrinogen is a 340-kDa glycoprotein synthesized in the liver, with a multitude of functions including fibrin clot formation, non-substrate thrombin binding, platelet aggregation and fibrinolysis.[5] It is composed of 2 sets of 3 homologous polypeptide chains known as A-Alfa, B-beta and gamma chains that assemble to form ahexameric structure. Each polypeptide is encoded by a distinct gene, *FGA*, *FGB*, and *FGG*, respectively, clustered in a region of 50 kb on chromosome 4q28-31. [6]

The primary physiological role of fibrinogen occurs when it is converted to insoluble fibrin, the final step in the coagulation cascade, with the formation of afibrin clot. The fibrin clot has an essential role in limiting bleeding at sites

of blood vessel injury. It also provides the structure for assembly and activation of the fibrinolytic protein.

Congenital afibrinogenemia is the result of defective fibrinogen synthesis. Although mutations have been found in all 3 of the fibrinogen genes, the most common defects are aberrant splicing and deletion mutations in the fibrinogen alpha gene.

In patients with afibrinogenemia, umbilical bleeding, soft tissue and mucosal bleeding, menorrhagia, gingival bleeding may be observed frequently. Gastrointestinal and urinary tract bleedings are observed less frequently. Intracranial bleeds occur rarely. Although bleeding may occur after trauma and surgery, spontaneous bleeding is rare.

Acute hemorrhagic episodes can be treated with either fresh frozen plasma or cryoprecipitate or fibrinogen concentrate. Each cryoprecipitate bag contains 100 to 150 mg of fibrinogen. Cryoprecipitate is given as one to one and a half units per 10 kg.

The half-life of fibrinogen is 2-4 days and frequentinfusions are usually not necessary.Recommendations regarding target levels for treating bleeding range from 30-50 mg/dL to 100 mg/dL.[7]Wetreat bleeding episodes with cryoprecipitate as fibrinogen concentrate is not available to us.

In our case series, 3 patients presented with bleeding symptoms. Out of which one patient had intramedullary bleed in meta-diaphysis of femur.She responded to cryoprecipitate infusion. In literature, only few cases have been reported with intraosseous bleeding. [8, 9]

One patient presented with bleeding as well as thrombosis. Paradoxical arterial or venous thromboses have been reported to occur due to underlying thrombophilia or after infusion of fibrinogen-containing preparations. [2]In our patient, thrombotic complications occurred at a young age and in the absence of fibrinogen infusion or circumstantial risk factors. We did not anticoagulate the patient as it was a chronic thrombosis. The management of thrombotic complications in patients with afibrinogenemia is problematic because of their bleeding tendency. Some authors proposed the concomitantadministration of replacement therapy with low-dose heparin.[10]In patients who develop recurrent thromboticepisode despite treatment with heparin and aspirin, treatment with direct thrombin inhibitorcan be effective.[11]

Isolated case reports ofrecurrent abortions in afibrinogenemic women are mentioned in the literature.Ourpatient had eight abortions till date. [3]Successfulpregnancies are possible in patient with afibrinogenemia if treated with fibrinogen concentrate or cryoprecipitate.[12, 13]Replacement therapy should be started at 5th week of gestation and continued throughout the pregnancy aiming at fibrinogen levels >1.0 g/L. [13]

Another patient developed inhibitor on repeated transfusion. Only 3 cases of large deletions in fibrinogen genes have been reported in English literature so far, the largest being 15 kb [15]. But none of these patients had developed inhibitors. This is first reported case of afibrinogenemia with inhibitor so far.

Prenatal diagnosis is possible when both parents are known heterozygotes for afibrinogenemia mutations or already havean affected child. The genetic mutations responsible for this defect have been characterized in only a few of the reported cases like FGA deletions, FGB missensemutations and an FGG mutation, most common being the mutations in the FGA gene.[14, 15]We have identified mutations in 2 patients involving FGB gene. We could not perform this study in 4 of our patients due to the unwillingness of family members.

4. Conclusion

In afibrinogenemia, bleedingsymptoms are qualitatively different. All our seven patients had varied and sometimes rare manifestations of afibrinogenemia.Patients with afibrinogenemia should ideally be referred to and registered with a haemophiliacentre. Risks of bleeding as well as thrombosis must be considered in these patients. Pregnancy is best managed in centres with available Haematology expertise.

5. Competing interests

The authors declare that they have no competing interests

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