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Congenital Afibrinogenemia: Case Report and Literature Review

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Abstract: ***Introduction:*** congenital afibrinogenemia is a rare autosomal recessive disease caused by markedly reduced or absent synthesis of fibrinogen. Consanguinity is common in affected family. Clinical manifestations range to minimal or moderate bleeding to catastrophic haemorrhage. ***Case presentation*:** We report a case of a female child, 07 months of age, Admitted to emergencies for ecchymosis and repetitive bleeding at vaccine injections sites. Biologic exploration found congenital afibrinogenemia. ***Conclusion*:** Congenital afibrinogenemia is a rare disease, which can be revealed at the neonatal stage when the umbilical cord is dropped. Its diagnosis is based on a balance of haemostasis disrupted with a normal level of coagulation factors, besides fibrinogen which is indosable. Prenatal diagnosis is currently possible by the molecular diagnosis. Gene therapy is a therapeutic approach for the future.
Keywords: Bleeding; afibrinogenemia; Congenital; screening.

INTRODUCTION

Congenital afibrinogenemia is a dyscrasia that is due to a congenital fibrinogen synthesis deficiency. It is a rare bleeding disorder [1]: about 150 families have been reported throughout the world since the first German observation published by Rabe in 1920 [2]. Fibrinogen is a glycoprotein present in plasma with a variable concentration rating between 1.8 and 4.1 g / L [3]. It has an important role in hemostasis where it intervenes at several levels: primary hemostasis by binding the glycoprotein IIbIIIa, platelet aggregation ... In clotting, it represents factor I because it's the key element of the clot. In clot degradation, it activates the plasmin enzyme that catalyses the reaction of fibrinolysis. In addition to these functions, it plays a crucial role in maintaining the integrity of the vascular wall through these molecular interactions. It is important in maintaining the blood viscosity and also intervenes in the mechanisms of diapedesis, nidation, and tissue repair [4].

The fibrinogen deficiency can be revealed in the neonatal age by a haemorrhage the gravity variable when cutting the umbilical cord. Although its diagnosis is easily evoked in the presence of incoagulable blood and an undesirable level of fibrinogen, its management is difficult and is mainly based on the administration of fibrinogen [1].

On the occasion of a new observation, we propose to make a clinical, therapeutic and especially to address the biological problems of dysfibrinogénémies.

CASE PRESENTATION

It is a 7-month-old infant, originally from Dakhla, admitted to the hematology department for ecchymosis, and repeated haemorrhages at the sites of vaccine injections, born from a first-degree consanguineous marriage. In his family history we find the notion of death of 4 brothers at an early age, one of them died by a haemorrhagic syndrome at the fall of the umbilical cord on 4th Day of life, The etiology of death of the other brothers has not been determined, but it was between 1th Day and 7th Day of life in a table of mucocutaneous pallor, without externalized haemorrhage.

At the anamnesis we find that it had a low abundance haemorrhageat the fall of the umbilical cord on the 4th day of life, not stopped by local haemostatic gestures and had necessitated the transfusion of fresh frozen plasma (FFP). Evolution thereafter was marked by the appearance of ecchymosis, and permanent modest bleeding at the puncture points. At the time of his admission; the infant appeared to be in excellent general condition, apyretic. There was a multiple diffuse ecchymosis, on the upper and lower limbs.

The detailed examination reveals no malformation and shows no abnormality in different organs. The clinical presentation had first evoked a haemostasis disorder.

His complete blood count was as follows: hemoglobin: 13.4 g/dl, leucocyte count: 7420/mm3, trombocyte count: 2225, 000/mm3; and the peripheral blood smear revealed abundant and clustered trombocytes. The coagulation profile revealed an incoagulable prothrombine time (PT) and Activated Partial Thromboplastin Time (aPTT). Factors II, VII, VII, IX, X of the coagulation were normal, but fibrinogen was indosable, as were the fibrin degradation products (FDP) and D-dimer Table 1.

The diagnosis was congenital afibrinogenemia, and the family was made aware of the various precautions to be taken in everyday life, including dental care, medicines and contraindicated sports. The evolution was marked by the occurrence of several haemorrhagic incidents: epistaxis, ecchymosis,, for which the child received fresh frozen plasma (FFP). Since the child is in good general condition. A screening was done for some family members Figure 1.

Table-I: biological test realised

Test	Patient	Common values
- platelets (/mm3)	225.000	150-450
- prothrombine time (%)	Incoagulable	80-120
-Activated Partial Thromboplastin Time (S)	incoagulable	34
-Factor I (fibrinogen) (%)	indosable	50-150
-Factors II , VII ,VIII , IX ,X	Normals	50-150
- the fibrin degradation products (µg/ml)	Absent	< 10
- D-dimère (µg/ml)	Absent	<500
-groupage	O+	

DISCUSSION

Epidemiology

Congenital afibrinogenemia is one of the rare disorders of coagulation, because only 150 cases have been reported since the first German observation published by Rabe 1920. The prevalence of the disease is currently estimated at 1 case per 1 million inhabitants; and according to the latest figures of the World Federation of Hemophilia published in 2009 [1], about 7% of rare haemorrhagic disorders are due to fibrinogen deficiency [2]. Thus, 67 families were known to carry this dyscrasia until 1972, and 83 families from 1972 to the present day [3]. The disease is transmitted according to the autosomal recessive mode, consanguinity is reported in 50% of the families discovered and the parents of the patients are unharmed [4].

Clinical Study

It is a condition that affects both sexes. It is seen more frequently in cases of consanguinity [6, 7]. The diagnosis can be evoked from the anamnesis: notion of umbilical bleeding (this sign was found and even imposed a transfusion of FFP in our patient) or episode of bleeding identical to that of the patient among the ascendants or siblings [5]. In congenital afibrinogenemia, bleeding may vary, from mild to severe. The intervals between episodes of bleeding can be very long. Several types of bleeding have been described: ecchymosis, haemorrhage following circumcision, gum bleeding, epistaxis, gastrointestinal haemorrhage, genitourinary or intracranial haemorrhage and rupture of the spleen.

About 20% of people with Afibrinogenemia have haemarthroses. Due to this particular aspect, the disease can be confused with hemophilia A or B. The haemorrhagic complications that are encountered in cases of congenital afibrinogenemia are most often the result of trauma, sometimes minimal, and which can even go unnoticed [8]. On the other hand, spontaneous bleeding is rare [8]. Although afibrinogenemia is congenital, bleeding may occur at a lateage, around the second decade of life [8].

A case of bilateral spontaneous dissection of the vertebral arteries in a young woman aged 28 is reported by Garcia-Monco and *et al*. [9]. Spontaneous rupture of the spleen or intracerebral spontaneous bleeding may occur [7, 8, 10, 11]. These spontaneous bleedingsare easily treated if discovered early. But most often, the gap between the clinic and medical imaging causes a delay in the initiation of treatment. Thus, in the presence of a strong clinical presumption of bleeding despite normal scanner images, replacement therapy should be started immediately and continued [11]. Bleeding from congenital afibrinogenemia, whether traumatic or spontaneous, responds favorably to replacement therapy: fresh frozen plasma or concentrated viro-inactivatedof fibrinogen. This concentrate is obtained from human plasma and essentially contains fibrinogen. The concentrate is subjected to a viral inactivation process, which eliminates viruses such as HIV and hepatitis A, B and C [6, 7, 9, 11, 12].Surgical treatment is exceptional and may worsen the patient's condition in the event of poor indication. The severity of the disease is related to the risk of visceral hemorrhage, especially intracranial hemorrhage and spleen rupture.

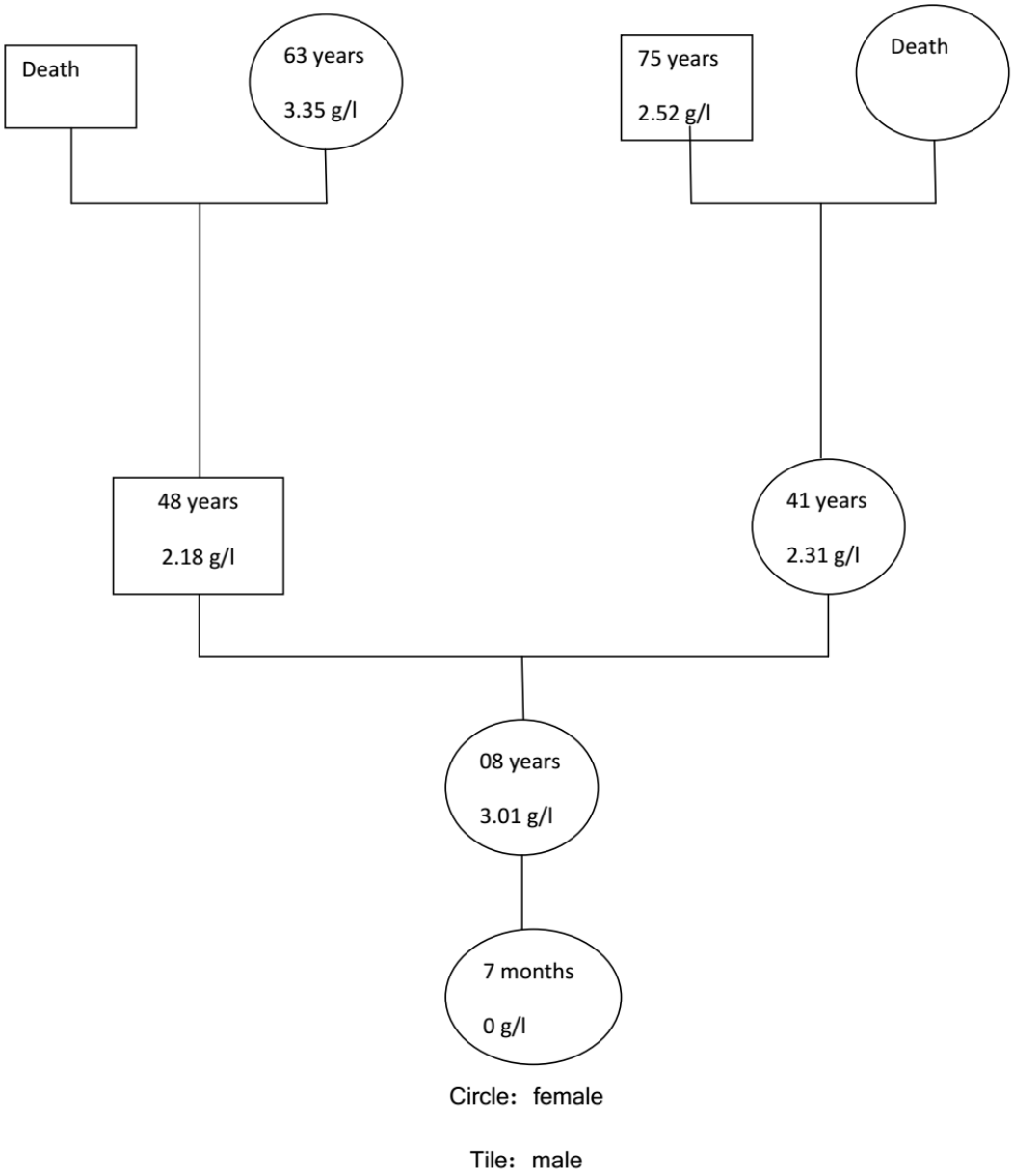

Fig-1: Age and fibrinemia of great parents and parents

Biology

The diagnosis of the disease is confirmed by biology. Three classes of inherited fibrinogen abnormalities have been identified: dysfibrinogenemia, hypofibrinogenemia and afibrinogenemia. Dysfibrinogenemia are qualitative abnormalities due to the presence of abnormal fibrinogen; Most of the affected individuals are asymptomatic and the discovery is often fortuitous. In 20% of the patients, the symptoms are haemorrhagic signs in 25% of cases or thromboembolic manifestations (thrombophlebitis, pulmonary embolism ...), sometimes causing the severity of the disease [1].The hypofibrinogénémies are characterized by a partial deficiency of fibrinogen often asymptomatic and can be expressed by bleeding after trauma or in case of coexistence of another disorder of hemostasis. Dys- and hypo- fibrinogenemia are differential diagnoses of afibrinogenemia which is the most extreme form of quantitative fibrinogen deficiency [1, 4]. The haemostasis results show incoagulable blood with a normal platelet count, bleeding time and activated partial thromboplastin time (aPTT) are very elongated, very low prothrombin time (PT). In case of afibrinogenemia, the fibrinogen is indosable, as in our case, whereas in hypofibrinogenemia its rate is low detectable by immunoassay techniques. The absence of FDP excludes the hypothesis of intravascular coagulation Disseminated [4,5].

Fibrinogen is a complex glycoprotein composed of three subunits (chains a, b and g) which are coded by genes located on chromosome 4 (4q28-q31) [5, 9]. The first genetic abnormality responsible was described in 1999 by Neerman-Arbezetal. This was

a deletion of the majority of the FGA gene (gene encoding the chain) in four members of a Caucasian family [10, 11] since many other mutations have been described [12,13]. The two most frequent mutations are FGAIVS4 + 1G> T (c.510 + 1G> T) and FGA11-kb deletion, which is present in about 40% of patients. Molecular analysis may be particularly useful in dysfibrinogenemia because some mutations are predictive of hemorrhage, while others may predispose the individual to develop thrombotic complications [1]. The genetic study was unfortunately not possible in the child of our observation or in his relatives.

Management is based on the prevention and administration of fibrinogen, both in the haemorrhagic period and in prophylaxis. Gene therapy is a therapeutic approach of the future, the preparatory work of which is currently under way [1,5]. Preventive treatment is essentially based on the avoidance of sports practices that are responsible for even minimal trauma; parent education is the first step to be taken .In case of bleeding, the evacuation of post-traumatic hematomas and the administration of fibrinogen (20 -30mg / kg every 10-14 days) to maintain a level of fibrinogen > 0.5-1 g / l.

CONCLUSION

Congenital afibrinogenemia is a rare disease of hemostasis, and its transmission is autosomal recessive, which can be revealed at the neonatal stage when the umbilical cord is dropped. At a distance from this period, it evolves in a latent mode, on which may be grafted haemorrhagic problems. Its diagnosis is based on a balance of haemostasis disrupted with a normal level of coagulation factors, besides fibrinogen which is indosable. Prenatal diagnosis is currently possible by the molecular diagnosis. The management is difficult and based to the prevention and administration of fibrinogen, both in the haemorrhagic period and in prophylaxis. Gene therapy is a therapeutic approach for the future.

List of abbreviations

FFP: Fresh frozen plasma.
PT: prothrombine time
APTT: Activated Partial Thromboplastin Time
FDP: Fibrin degradation products (FDP)

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