CONGENITAL AFIBRINOGENEMIA

A Case Report and Therapeutic Trials

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Congenital afibrinogenemia is a fairly rare molecular disease. Up to 1957 there were only 32 reported cases in medical literature.[1] Since then, more reports have been published. Bommer, et al, collected 55 reports of congenital afibrinogenemia up to 1959.[2] Between 1959 and 1965, 34 more reports of this condition were published, bringing the total to 89.

Although patients with congenital afibrinogenemia are lacking the most important coagulation factor for fibrin formation in their circulation, spontaneous bleeding episodes occur less often in this condition than in different kinds of hemophilia. Also, hemorrhages caused by this condition can easily be controlled by increasing the plasma fibrinogen level over 100 mg per cent by the administration of plasma or fibrinogen fractions.

Epsilon amino caproic acid (EACA) and some hormones have recently been shown to be effective in decreasing fibrinolytic activity.[3-11] We have sought to determine the effect of EACA, corticosteroids and estrogenic hormones on the fibrinogen level of our patient. Because of the rarity of the disease, the interesting family history and therapeutic trials, we felt this case would be useful to report.

Case Report

This 11 year old girl has been followed at our clinic since she was five years old. Five or six days after her birth, it was reported that she had had bleeding from the cord stump. Since then, she has had several bleeding episodes following the eruption of teeth and ecchymosis following trauma. Seven days prior to her last admission she had profuse bleeding from a small ulcer on her left leg, which had been produced by a mild trauma.

The patient's parents are second cousins, and there are several bleeders among the relatives of both parents. Her six siblings (three sisters and three brothers) died of bleeding between the ages of six and 24 months (Figure 1).

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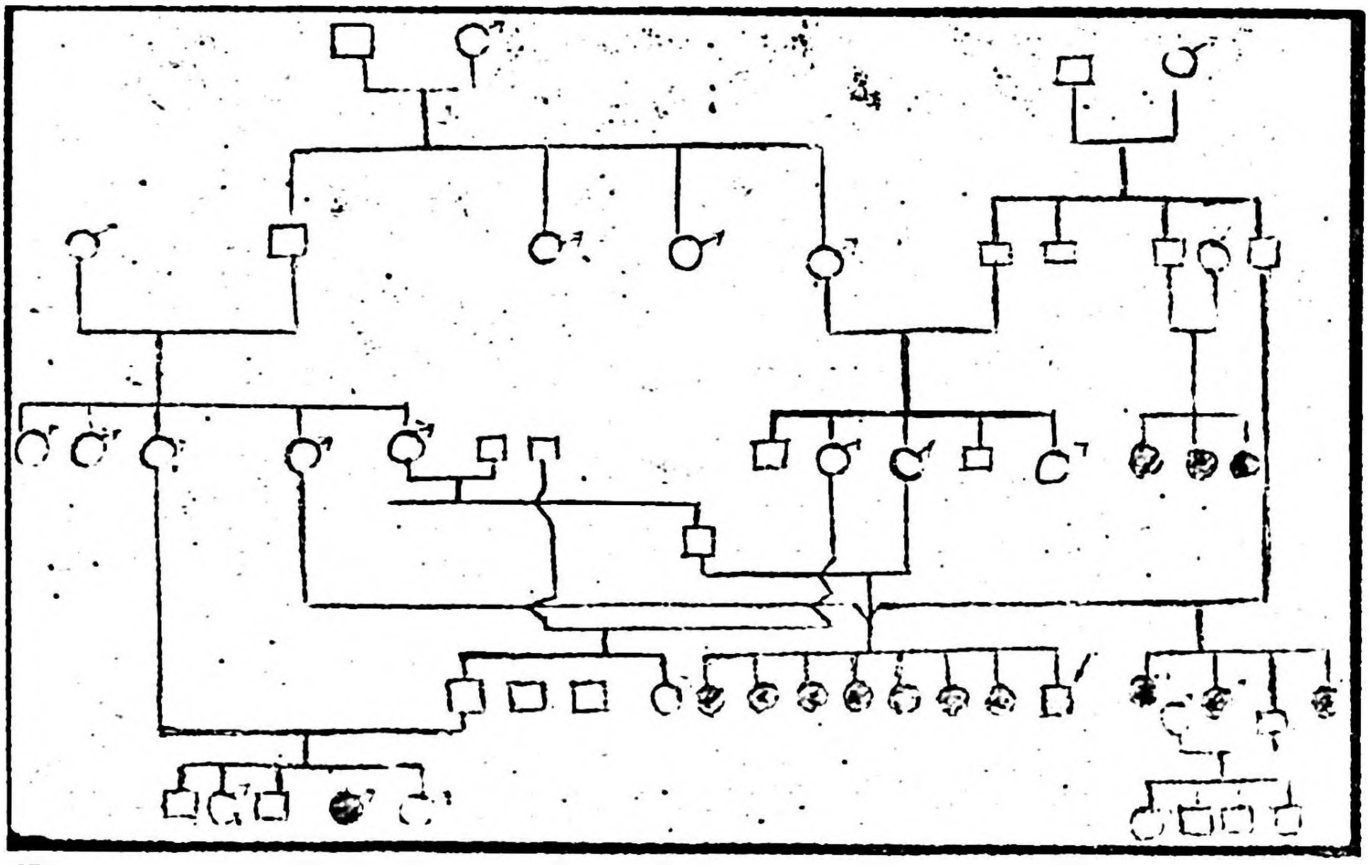

Figure 1. Patient's family tree. Arrow in lower right corner indicates propositus.

Physical Examination : The patient was a pale looking, shy, preadolescent girl. She had several areas of ecchymosis on her legs, and freckles were noted on the face. A grade I/IV systolic murmur was heard in the precordial area. Her liver was felt one cm below the right costal margin. Her I. Q. was 71. The remainder of the examination was unremarkable.

Laboratory Examination : Hemoglobin, 6.95 mg per 100 ml; WBC, 8,600 per cmm with a normal differential count. Sedimentation rate, 4 mm per hour. Urinalysis and liver function tests: total bilirubin, 0.7 mg/100 ml, with a direct value of 0.3 mg/100 ml. Total protein: 6.6 mg/100 ml; SGOT, 18 u; cephalin flocculation, 2+; Thymol turbidity, 2.5 u; cholesterol, 240 mg %, were all within normal limits.

Analysis of plasma protein electrophoresis was carried out using a filter paper strip technique in a Jouan apparatus and produced the following results; albumin, 52.8 %; globulins, alpha one, 3.1 %; alpha two, 10.8 %; beta, 20.6 %; gamma, 12.7 %. The fibrinogen peak, which had a mobility between that of gamma globulin and beta globulin, was not seen in the electrophoretic pattern of the patient's plasma. The results of the coagulation studies are summarized in Table 1. There was no fibrinolysis, and no circulating anticoagulants could be demonstrated. After the addition of fibrinogen* (in a concentration of 150 mg %) Quick prothrombin time, PTT and TGT were completely normal. Screening test for factor XIII, after fibrinogen addition, gave normal results.

Her iron deficiency anemia was treated with oral iron and she was given penicillin tablets, 400,000 units a day for eight days because beta hemolytic streptococci were cultured from her throat. She was given prednisolone, 50 mg/

* Warner-Chilcott fibrinogen was used.

TABLE 1

THE RESULTS OF COAGULATION STUDIES OF OUR PATIENT

Tests	Patient	Normal
Clotting time Lee, R.I., and White, P.D.: Am. J. Med. Sci. 145 : 495, 1913	did not coagulate	up to 13′
Bleeding time Ivy, A.C., Shapiro, P.R., and Melnick, P.: Surg., Gynec., and Obstet. 60 : 781, 1935	5.5′	8′
Tourniquet test	negative	negative
Platelet count	288,000	200,000-400,000
Quick, Prothrombin time Quick, A. J.: J. Biol. Chem. 109 : 73, 1935	more than 5′	13″
after fibrinogen addition*	14″	—
P.T.T.** Rodman, N.F., Barrow, E.M., and Graham, J.B.: Am. J. Clin. Path.: 29 : 525, 1958.	more than 5′	50″-100″
after fibrinogen addition	102″	—
Fibrinogen (level in serum was 25.7 % by this method) Ratnoff, O.S., and Mehzie, C.: J. Lab. Clin. Med. 37 : 316, 1951	30 mg %	250-400 mg %
Circulating anticoagulant (after adding fibrinogen or normal plasma)	(—)	(—)
Circulating fibrinolysis (after adding fibrinogen or normal plasma)	(—)	(—)
TGT *** Biggs, R., and Douglas, A.S.: J. Clin. Path. 6 : 23, 1953	normal	normal
Plasma, heated up to 60 C	no turbidity	turbidity
0.1 patient's plasma + 0.1 thrombin	did not coagulate	fibrin formation
Factor XIII **** (after addition of fibrinogen) Josso, F., Prou-Wartelle, O., Alagille, D., and Soulier, J.P.: Nouv. rev. Franç. d' hemat. 4 : 267, 1964	(+)	(+

* Fibrinogen concentration was raised to 150 mg % in all tests by fibrinogen
** Partial thromboplastin time.
*** Thromboplastin generation test.
**** Fibrin stabilizing factor.

day for 13 days without any changes in the fibrinogen level. Following this treatment, Ipsilon R* was administered (200 mg/Kg/day) for eight days by mouth and no increase in fibrinogen level was observed. After the administration of Lyndiol R** (2 tablets per day) for one month, her fibrinogen level was increased more than 100 per cent from the initial level of 30 mg % (to 77.5 mg %).

Although they had no history of abnormal bleeding, the plasma fibrinogen levels of both parents were found to be markedly decreased (father's, 176 %; mother's, 122 mg %).

Discussion

There are generally two types of afibrinogenemia, congenital and acquired. Most cases of the acquired type of hypo or afibrinogenemias are reported in adults and are caused by burns, hepatic cirrhosis, neoplastic diseases, obstetric complications, and a variety of hematologic or miscellaneous disorders. [12, 13] However, acquired afibrinogenemia caused by acute idiopathic fibrinolysis has also been reported in the newborn period.[14]

In our case, liver function tests were normal and no evidence of active fibrinolysis, intravascular clotting, or multiple hemangiomata, which might cause hypofibrinogenemia in this age group, could be detected.[15, 16] The presence of a bleeding tendency since birth and the family history substantiate the diagnosis of a congenital disease. Low fibrinogen levels of both her parents add to the evidence in favor of the congenital nature of the disease in this patient.

Congenital afibrinogenemia is generally inherited through an autosomal recessive gene, which causes a disturbance of fibrinogen synthesis in the liver.[12, 17 - 20, 22] Although the liver may not be the only organ involved, it is the most important site for fibrinogen synthesis. It is conceivable as has been suggested, that these patients are not entirely without fibrinogen, but that the amount was not detectable by our methods. Some authors have reported that, without being symptomatic, the fibrinogen levels of parents of the patients were lower than normal.[1, 17, 19, 20] Several cases of afibrinogenemia among siblings have also been reported.[1, 19, 21 - 23] Hypofibrinogenemia was found in both the parents of our patient. However, we don't know whether her siblings, who had a history of bleeding and died within the first two years of life, actually had afibrinogenemia. We

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* Ipsilon R (epsilon amino caproic acid) was kindly supplied by Fako İlâç Sanayi Company.

** Lyndiol R was supplied by Organon and contains 2.5 mg lynestrenol progesteron and 0.075 μg of methoxyaethinyloestradiol (estrogen).

consider it a strong possibility, however. Although afibrinogenemia is a fairly rare disease, in this family there were several interfamilial marriages, which may be the reason that so many bleeders were seen. We observed another patient with congenital afibrinogenemia, a close relative of our patient, who died after severe bleeding caused by a trauma.[26] So far, these are the only reported cases of congenital afibrinogenemia in Turkey.

Fibrinogen is normally distributed equally between interstitial fluid and plasma. Gitlin and Borges have demonstrated a deficit of tissue fibrinogen also, in this disease.[24] Despite the lack of a fibrin net, however, healing of wounds in these patients is not retarded. Although bleeding time varies widely in this condition, it is usually within normal limits as it was in our patient.[2, 19] The low sedimentation rate in spite of a moderate degree of anemia must be a result of afibrinogenemia.

Factor XIII, fibrin stabilizing factor, has been determined in at least two cases of congenital afibrinogenemia and was found to be normal.[23] Factor XIII activity, which could be determined after adding fibrinogen (concentration of 150 mg %) or normal plasma, was also normal in our patient.

Lewis and Ferguson [25] found that by administering plasma transfusions, the patient's plasma fibrinogen level could be raised promptly to the level at which clot-formation would occur and would decline subsequently by one half in four days. The half-life of fibrinogen *in vivo* has been shown to be four to five days.[17, 19, 24] For the control of bleeding in this condition, plasma, Cohn fraction I and fibrinogen fractions have been used. Trauma and cuts are potentially more dangerous for these patients.

It has been suggested that the fibrinogen synthesis is not absolutely absent in this disease. Since high fibrinogen levels have been observed in some patients on corticosteroid treatment,[27] we gave corticosteroids and EACA, which has been used in the treatment of acquired afibrinogenemia,[7, 11] to decrease the normal fibrinolysis and in this way increase the fibrinogen concentration, without any effect.

In 1953, Tagnon, et al, reported that by the administration of estrogenic hormones, with the disappearance of fibrinolysis, the deficiency of fibrinogen was corrected in a patient with cancer of the prostate.[3] The opposite effect of testosterone is also known.[3, 5] Recently, Brakman and Astrup, and Shaper, et al, have shown the effect

of oral contraceptives, pregnancy and puerperium on the fibrinolytic system and fibrinogen levels in the blood.[4, 10] With their results in mind, we used Lyndiol, a contraceptive drug, in treating this pre-adolescent girl, and were able to increase the fibrinogen level of her blood by 100 per cent within one month.

This is only a preliminary report on the effect of Lyndiol treatment in congenital afibrinogenemia. More detailed studies are being prepared.

Summary

The case of an eleven year old girl with congenital afibrinogenemia is reported. There are several possible afibrinogenemic individuals in this family. The fibrinogen levels of both parents were very low. Our patient was given Lyndiol R (an oral contraceptive drug) and her fibrinogen level was increased by more than 100 per cent within one month. The literature about this condition is briefly reviewed.

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