Congenital Deficiency of Factor XIII

Şinasi Özsoylu, M.D.* / Behice Yamak, M.D.**

Factor XIII, or the fibrin stabilizing factor (FSF) has been known and investigated in vitro for more than 20 years,[1] but hemorrhagic diathesis due to congenital deficiency of this factor was first described in 1960 by Duckert, Jung and Shmerling.[2] Since then, 22 more cases have been reported.[3] The following is the first instance of this defect described in Turkey.

Case Report

A.A. (TTF 68/70950) a four-month-old Turkish boy, was referred by another hospital to our hematology clinic for work-up on his hemorrhagic diathesis. He was the product of a full-term gravida II, para 1, non-complicated pregnancy. At 12 days of age, two days after the cord had fallen off, he started to bleed from the navel. Local treatment was ineffective and the bleeding was controlled only after whole blood transfusion. A month later the patient had jaundice, with a temperature elevation to 41 °C, for two days. On the sixth day of jaundice, he began to have generalized convulsions which lasted for four hours. After that, paraplegia was noticed by the family, and the infant was hospitalized; subarachnoid bleeding was documented by cerebrospinal fluid (CSF) examination. Twenty-four hours after lumbar puncture, bleeding started from the site of the needle, and did not stop until a blood transfusion had been given. The patient was referred to our hospital because the initial coagulation studies did not indicate any hemorrhagic diathesis.

Physical examination revealed a fairly well-nourished boy with flask paraplegia. He showed vertical nystagmus. Deep tendon reflexes of the lower extremities were not elucidated, and the Babinski sign on both sites was indifferent. His liver was three cm below the right costal margin, but the remainder of the examination was unremarkable.

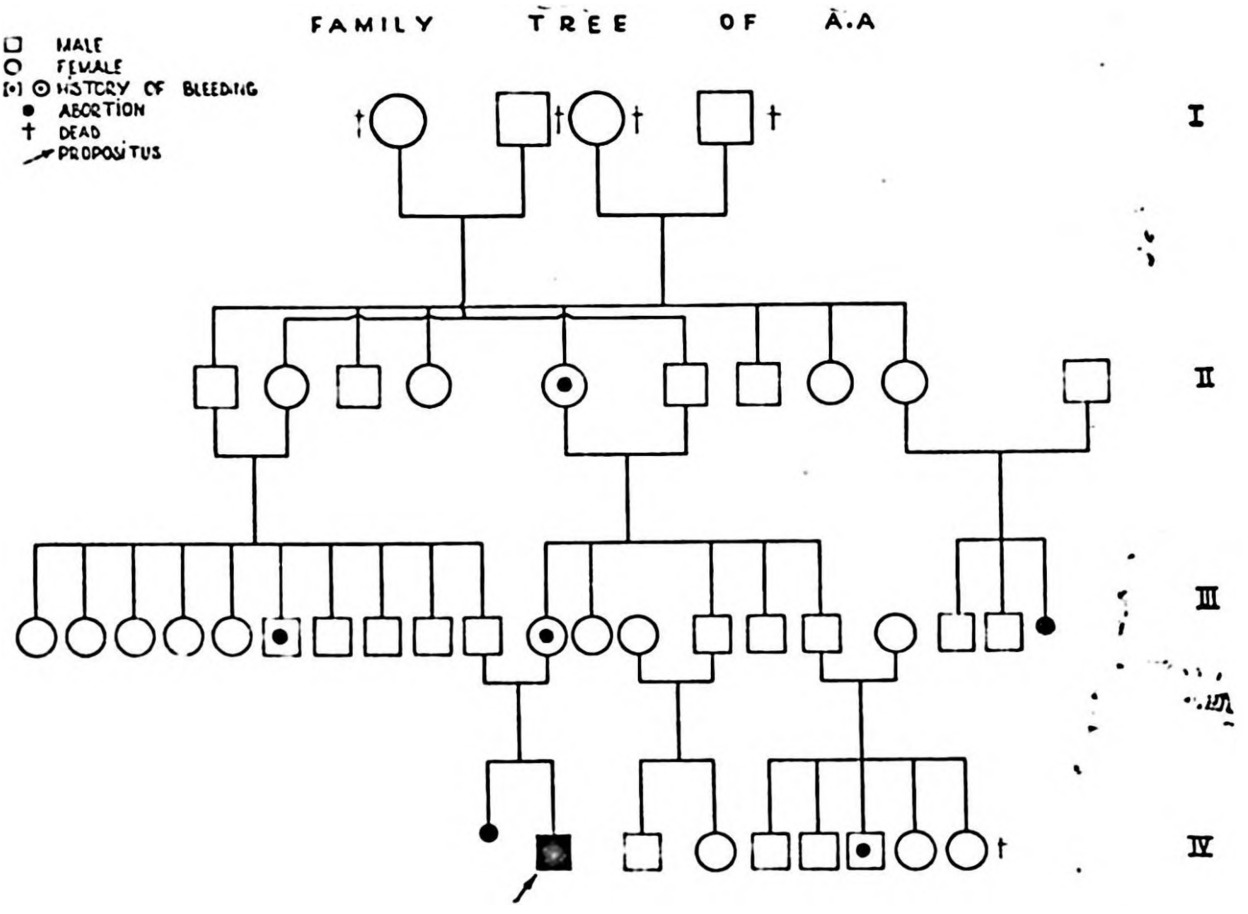
From the Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

* Associate Professor of Pediatrics and Hematologist.

Hemoglobin was 8.6mg/100 ml, hematocrit 25 per cent, and WBC 8,300 cmm, with a normal differential count for his age. Platelets were abundant on the peripheral smear.

As can be seen from his family tree (Figure 1), the patient's mother and father were first cousins. The mother had bleeding following her first coitus which continued for two days, and her first pregnancy was interrupted by spontaneous abortion with severe bleeding lasting for a month. The maternal grandmother also had excess bleeding after her last delivery.

Figure 1



Methods and Results

The examination included Ivy bleeding time,[4] petechiometer, clotting time (the Lee-White method), Quick prothrombin time,[5] dosage of fibrinogen,[6] partial thromboplastin time (PTT)[7], and thromboplastic generation time (TGT).[8] The study of clot stability (factor XIII) was performed by the method of Josso et al,[9] using one per cent monochloracetic acid (the results are expressed from - to ++++ according to the size of the remaining clots after 24 hours' incubation at room temperature).

The results of the coagulation studies of the propositus and his parents are summarized in Table 1.

TABLE 1

CLOTTING TEST

Test	Normal range	Propositus	Father	Mother
Quick Prothrombin time	12 sec.	12	12	12
PTT	60-120 sec.	65	102	109
Bleeding time	6 min.	3	—	—
Clotting time	7 min.	4	3	3.5
Clot retraction (after 1 hour)	2-4+	3+	3+	3+
Petechiometer	neg.	neg.	—	—
TGT	normal	normal	—	—
Fibrinogen	200-400	250	218	283
Factor XIII	—	++++	++	++

Since these studies indicated clot stabilizing factor deficiency in the propositus, the following mixtures were made to find an inhibitor effective on the patient's factor XIII, and to try to assay the parents' factor XIII (Table II).

Discussion

FSF is a clotting factor present both in plasma and in serum (though less in the latter).[10] Together with calcium ion, it promotes strong bonds between the fibrin molecules, with the formation of a clot capable of normal hemostatic function. In vitro, fibrin polymers become insoluble in 5M of urea or one per cent monochloracetic acid solutions. This factor is also shown in normal platelets, but not in erythrocytes or leukocytes. However, biological activities and certain chemical properties indicate that plasma platelet factor XIII is a distinct component.[11] In the absence of factor XIII, although the quality of the fibrin is defective, fibrin formation normally occurs.

Our patient had the classic symptoms of factor XIII deficiency; prolonged umbilical bleeding in the neonatal period, late bleeding after cuts, and even cerebromeningeal hemorrhage, all controlled by whole blood or plasma transfusion. Coagulation studies in this case were within the normal limits, except for an abnormal one per cent monochloracetic acid solubility test which indicated the diagnosis. Although an acquired inhibitor against this factor has been reported, the mixture studies of the patient's plasma and normal plasma were not compatible with this possibility.[12 13]

TABLE 2

MONOCHLORACETIC ACID (I%) SOLUBILITY TESTS*

Tube	1	2	3	4	5
Patient's plasma (ml)	0.1	0.1	0.1	0.1	0.1
Normal plasma (1/10) (ml)	0.05				
Normal plasma (1/100) (ml)		0.05			
Mother's plasma (1/10) (ml)			0.05		
Father's plasma (1/10) (ml)				0.05	
Veronal buffer (ml)					0.05
CaCl2 0.05 M (ml)	0.05	0.05	0.05	0.05	0.05
Monochloracetic acid (1%) (ml)	1.5	1.5	1.5	1.5	1.5
State of clot					
1 hour	—	++	+	+++	++++
24 hours	—	++++	++	++++	++++

* Half plasma and reagents were used because the patient's plasma was not available. (Plasma dilutions were done with veronal buffer).

Since the propositus was four months of age, the low level of FSF cannot be explained by the low level observed at the neonatal stage.[3 14] In fact, factor XIII in the newborn period is not so low as to cause early bleeding from the cord, as happened in this case. Acquired factor XIII deficiency has been reported following liver disease and blood dyscrasias.[13] Although this patient had jaundice with infection two and a half months prior to coming to our clinic, no evidence of liver disease was found clinically or by laboratory tests, and the history of bleeding preceded the jaundice. The family history and probable heterozygosity of the parents do not leave any doubt about the congenital nature of this disease.

Following blood and plasma transfusions the child's subdural collection was evacuated by several taps without any more bleeding.

Summary

A four-month-old male infant with congenital deficiency of the fibrin stabilizing factor is described. He presented prolonged umbilical bleeding, and subdural and cerebromeningeal hemorrhage, all of which were controlled by whole blood transfusions. The coagulation studies in this case were within normal limits, except for the solubility of the clot in one per cent monochloracetic acid. By mixture studies the heterozygosity of both parents was also shown.

Acknowledgement

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