Congenital Deficiency of Fibrin-stabilizing Factor (Factor XIII): A Report of Four Cases (Two Families) and Family Members

By Mohammed A. Aziz and Azizur Rehman Siddiqui

Four patients with congenital deficiency of fibrin-stabilizing factor (factor XIII) from two families have been described. The mother and the sibs in one family and both parents in the other family were found to have varying degrees of factor XIII deficiency. The observations support the hypothesis of autosomal recessive inheritance of factor XIII deficiency.

The existence of a blood factor that rendered clots prepared from purified fibrinogen insoluble in weak acid and urea was reported by Robbins in 1944. Laki and Lorand confirmed this observation in 1948 and designated this factor as the "fibrin-stabilizing factor." In 1963, the International Committee on New Blood Clotting Factors accepted this entity as a distinct coagulation factor and gave it the designation factor XIII. Patients with factor XIII deficiency have a tendency to bleed and show poor wound healing. In these patients, the usual tests for blood coagulation give normal results except for a considerable degree of crumbling of the clot and a striking diminution of the amplitude of the thromboelastogram. The diagnosis is confirmed by the rapid dissolution of the clot obtained by recalcification of the plasma in a 5 M urea or a 1% monochloroacetic acid solution. The factor XIII deficiency has been documented in at least 44 individuals from 27 families, including a single case from Pakistan reported by Zahir from this laboratory. In this communication, four additional cases of bleeding disorders associated with the fibrin-stabilizing factor (factor XIII) deficiency from two families will be reported.

MATERIALS AND METHODS

The coagulation studies were carried out according to the methods of Hardisty and Ingram, but plasma fibrinogen level was determined according to Quick. For the demonstration of clot solubility, blood was collected into one-tenth volume of 3.8% sodium citrate. The specimen was centrifuged immediately at 3000 rpm for 15 min, and the plasma was separated. To 0.2 ml of plasma an equal volume of 0.025 M calcium chloride was added and incubated at 37°C for 30 min for the formation of a clot. The clot was then tapped loose and transferred with a loop into a test tube containing 10 ml of 5 M urea.

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solution. The tube was then kept at room temperature and inspected at intervals for complete dissolution of the clot.

CASE REPORTS

Case No. 1

I.H., a 3-yr-old boy, experienced the first episode of bleeding at the age of 2 wk when his umbilical cord fell off. The bleeding continued for 4 days, and the patient was hospitalized. Blood transfusion was not necessary. Since then he has had repeated bleeding episodes after minor injuries. There has been no history of bleeding into the joints. The bleeding episode during this examination started when a scab fell off from his upper lip. He continued to bleed for 6 days before he was brought to the hospital. At the hospital bleeding stopped after local treatment in 4 days.

The family history revealed that one sister (case 2) out of 12 siblings also suffered from the bleeding disorder. The patient’s father reportedly died of a heart condition, and the mother is healthy and alive. Two of the siblings died at the age of 1 yr, but the causes could not be ascertained. The parents were distant relatives.

Physical examination of the propositus revealed numerous blue spots on his body and a Grade 2 systolic murmur along the left sternal border.

Laboratory investigation revealed a hemoglobin level of 9.3 g/100 ml and a slightly prolonged bleeding time. The only other apparent abnormality was demonstrated in the test for Factor XIII in which the patient’s plasma clot in 5 M urea solution dissolved within 40 min.

Case No. 2

N.J. is the 7-yr-old sister of case 1. The first bleeding episode occurred at the age of 2 when she received an injury on her forehead. She bled from this site for 3 days. Since then she has had several episodes of swelling of her knee joints, presumably from bleeding in the joints and repeated prolonged bleeding after minor injuries, but never any serious episode of bleeding requiring hospitalization.

Table 1. Factor XIII Assay of the Family Members of the Patients by Clot Dissolution Time*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Added Plasma</th>
<th>Per Cent Plasma Added for Correction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Normal*</td>
<td>0:30</td>
</tr>
<tr>
<td></td>
<td>Sib 1</td>
<td>1:02</td>
</tr>
<tr>
<td></td>
<td>Sib 2</td>
<td>0:48</td>
</tr>
<tr>
<td></td>
<td>Sib 3</td>
<td>0:45</td>
</tr>
<tr>
<td></td>
<td>Sib 4</td>
<td>0:48</td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
<td>0:35</td>
</tr>
<tr>
<td></td>
<td>Sib 5</td>
<td>0:40</td>
</tr>
<tr>
<td></td>
<td>Sib 6</td>
<td>1:10</td>
</tr>
<tr>
<td></td>
<td>Sib 7</td>
<td>1:00</td>
</tr>
<tr>
<td></td>
<td>Mother of cases 1 and 2</td>
<td>0:45</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
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<tr>
<td>4</td>
<td>Normal</td>
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<td></td>
<td>Father of cases 3 and 4</td>
<td>0:47</td>
</tr>
<tr>
<td></td>
<td>Mother of cases 3 and 4</td>
<td>0:40</td>
</tr>
</tbody>
</table>

* Time shown as hr:min.

One of the authors (ARS) donated normal plasma.
Physical examination revealed multiple bruises and a swollen left knee joint. The joint was not red or hot. The swelling apparently commenced 3 wk prior to the examination without any apparent trauma to the joint.

Laboratory investigations revealed a normal hemoglobin level and platelet count. Tests for blood coagulation gave normal results except for Factor XIII, which revealed that the patient's plasma clot dissolved in 5 M urea solution within 45 mm.

**Case No. 3**

R.M., an 18-yr-old male, was admitted to a local hospital with a painful swelling in the left iliac fossa and difficulty in walking. Surgical exploration revealed that the mass was a hematoma. The patient also passed blood in his urine. He received a blood transfusion while in the hospital, and the postoperative bleeding stopped. The past history included recurrent episodes of bleeding from minor cuts and bleeding following separation of the umbilical cord. Because of this bleeding tendency, his circumcision was delayed and was done at the age of 16. He bled profusely after the procedure and received blood transfusions.

The family history revealed that his parents are first cousins. Seven siblings, three sisters and four brothers, are dead. Excessive bleeding from the umbilical cord on the tenth day of life was apparently the cause of death in one sister, while four died of unknown causes during the first 2 wk of life. One sister died at the age of 12 yr and had a history of easy bruisability. She coughed up blood on many occasions. She was thought to have pulmonary tuberculosis, but the diagnosis was not confirmed. She died at home from profuse hematemesis. One brother died at the age of 6 yr apparently from gastroenteritis. Only a sister and brother are alive, the former being healthy and the latter (case 4) suffering from recurrent excessive bleeding from minor cuts.

Laboratory investigations revealed normal results except for the test for Factor XIII. The patient's recalcified citrated plasma clot dissolved in 5 M urea solution within 15 min; moreover, the clot appeared distinctly fragile and had a tendency to break up when taken out of the tube with a loop.

**Case No. 4**

R.M., a 20-yr-old male (brother of case 3) had a history of excessive bleeding following minor cuts and bruises since birth. Following separation of his umbilical cord and after circumcision he received blood transfusions due to excessive bleeding. Coagulation studies revealed normal results except for Factor XIII. The patient's recalcified citrated plasma clot dissolved in 5 M urea solution within 20 min.

**Family Studies**

The mother and ten sibs of cases 1 and 2 were also investigated and found to have normal hematologic values. The plasma clot of the mother and seven sibs were assayed for Factor XIII using the patients' plasma as substrate. Varying degrees of deficiency for Factor XIII were noted definitely in four sibs and possibly in the mother and three other sibs. The parents of cases 3 and 4 were studied and both were found to have reduced levels of factor XIII in their plasma (Table 1).

**DISCUSSION**

Fibrin-stabilizing factor (factor XIII) is a plasma protein that is hydrolytically converted by thrombin into a transpeptidating enzyme during the course of blood coagulation. This enzyme catalyzes the formation of $\gamma$-glutamyl-epsilon-lysine bridges between fibrin units leading to the production of a fibrin clot that is not soluble in 1% monochloroacetic acid or in 5 M urea.7,8

The hemorrhagic manifestation of factor XIII deficiency is quite similar in all cases reported in the literature. Severe umbilical bleeding has been the
commonest initial symptom. Ecchymosis, formation of hematomas, and prolonged hemorrhage following minor trauma are the other common symptoms. Delayed wound healing is not a common symptom, but it was the prominent feature of the first case with factor XIII deficiency described by Duckert et al.9 In the four cases described here, umbilical bleeding was the first symptom in three, while prolonged bleeding from minor trauma at the age of 2 was the first symptom in the other (case 2). In the latter case, the major manifestation in the ensuing years was repeated episodes of swelling of the knee joint presumably due to bleeding in the joint. Although hemarthrosis is a common feature in hemophilia, it has been described rarely in cases of factor XIII deficiency.

The beneficial effect of blood or plasma transfusion in these patients is well known. Two of our patients needed blood transfusions following bleeding from the umbilical cord and after circumcision. The other two cases never needed blood or plasma transfusions, but their hemostatasis was delayed compared to the controls.

The exact plasma level of factor XIII necessary to prevent bleeding is not known. It has been suggested that no more than 10% of the normal level is necessary to correct the defect in the patients’ plasma.9,10 In the present study, the addition of 0.6–1.2% of normal plasma to the clotting system rendered the patients’ plasma clot insoluble in the 5 M urea solution. This suggests that only about 1% of factor XIII is required to correct the defect in the patients’ plasma. Eight family members of cases 1 and 2, including their mother, were assayed for factor XIII. They were found to have varying degrees of factor XIII deficiency. Excessive bleeding from the umbilical cord was the cause of death of one sister at 10 days of life, and possibly one other sister also died of bleeding disorder. Thus, it is possible that at least two sisters of cases 3 and 4 had the factor XIII deficiency. Parents of cases 1 and 2 were distant relatives; presumably the father died of a heart condition. There was no history of death from excessive bleeding in this family. The patient (case 1) and his sister (case 2) appear to be homozygotes, while their mother and other sibs are probably heterozygotes. In the family of cases 3 and 4, the parents are first cousins and both had reduced levels of factor XIII. Out of seven dead sibs, two sisters died possibly of factor XIII deficiency. It is possible that cases 3 and 4 and their two dead sisters were homozygotes and the parents are heterozygotes for the factor XIII deficiency gene.

Ratnoff and Steinberg11 have suggested that the disease may be inherited in one of two ways: either as an autosomal recessive or as a sex-linked recessive. Recent family studies by Lorand et al.9, however, have shown that the factor XIII levels were equally decreased for both fathers and mothers in families with only affected males and in families with affected females, supporting the concept that congenital factor XIII deficiency is transmitted as an autosomal recessive trait. The present report of affected males and females and both parents (only one pair studied) showing varying degrees of deficiency supports the hypothesis of autosomal recessive inheritance.

First cousin marriages are very common in some sections of the Pakistani
population in this geographic area. It is, therefore, not unlikely that autosomal recessive traits like factor XIII deficiency may be encountered more frequently here than in other populations. In the limited period of the study, five cases, including the one reported by Zahir, have been studied from three families. The detection of so many cases in this preliminary survey suggests that the prevalence of factor XIII deficiency is, indeed, higher for the Pakistani population than in other populations studied previously.

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REFERENCES

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