ABSTRACT. Objectives. The objectives of this study were 1) to assess the importance of an early diagnosis for factor XIII (FXIII) deficiency, and 2) to investigate the molecular basis and mechanism(s) of disease in the patients under study.

Methods. The case histories of 6 FXIII-deficient patients were examined to assess the influence of early versus delayed diagnosis and replacement therapy. The nucleotide sequence of the FXIIIA gene was determined to identify the underlying mutations responsible for the bleeding diathesis in each patient. Molecular modeling was used to predict the mechanism(s) of disease causation for each mutation.

Results. All cases presented with umbilical hemorrhage. Patients 1 to 3 were diagnosed, and their prophylactic therapy was commenced in infancy. Diagnosis in patients 4 to 6 was considerably delayed and, as a result, they continued to suffer from many bleeding symptoms. The FXIIIA gene mutations identified in these patients were as follows: a homozygous GAA→AAA mutation in codon 102 (Glu102Lys) in patient 1 and a homozygous AGC→AGG mutation in codon 295 (Ser295Arg) in patients 2 to 6. These mutations segregate with disease and are absent from the normal population, suggesting that they are likely to be disease-causing sequence changes. Computer modeling indicates that both the Lys102 and Arg295 mutants are unable to fold correctly, and probably result in unstable FXIIIA molecules.

Conclusions. We demonstrate the importance of recognizing delayed umbilical hemorrhage as a presenting feature for congenital FXIII deficiency, and the value of early diagnosis and prophylaxis. The bleeding disorder of patient 1 was attributable to a homozygous Glu102Lys mutation in FXIIIA. A homozygous Ser295Arg mutation in FXIIIA was responsible for FXIII deficiency in patients 2 to 6. Pediatrics 2002;109(2). URL: http://www.pediatrics.org/cgi/content/full/109/2/e32; factor XIII deficiency, bleeding disorder, FXIIIA mutation, FXIIIA structure.

ABBREVIATIONS. FXIII, factor XIII; α2-PI, α2-antiplasmin; PCR, polymerase chain reaction; HIV, human immunodeficiency virus.

Delayed Umbilical Bleeding—A Presenting Feature for Factor XIII Deficiency: Clinical Features, Genetics, and Management

Rashida Anwar, PhD*; Adrian Minford, FRCPCH‡; Louise Gallivan, BSc*; Chi H. Trinh, PhD§; and Alexander F. Markham, FRCPATH*

Factor XIII (FXIII), the last enzyme in the coagulation cascade, is essential for normal hemostasis. Circulating as a proenzyme composed of 2 A subunits and 2 B subunits, FXIII requires calcium and thrombin for activation.1,2 Activated FXIII, a transglutaminase, catalyzes the formation of ε-(γ-glutamyl)lysine and cross-links between fibrin monomers, resulting in a fibrin clot that has greatly increased tensile strength.3–4 Another important action of FXIII is the cross-linking of α2-antiplasmin (α2-PI) to the α-chains of fibrin.5 When cross-linked to fibrin, α2-PI forms an active complex with plasmin. This is the primary mechanism for inhibition of fibrinolysis and protects the clot from early breakdown.

Duckert et al6 first described FXIII deficiency in 1960. They published a case report of a young boy with a severe bleeding syndrome, in whom all conventional clotting tests were normal but whose clots, prepared from recalcified plasma, were rapidly soluble in 5 M urea. Addition of a small amount of normal plasma rendered the patient’s clots insoluble. Moreover, transfusing the patient normalized clot solubility and corrected the bleeding diathesis. Since this first description, >200 cases have been reported in the world literature.7 Although rare, with an estimated incidence of ~1 in 108, congenital FXIII deficiency is one of the most severe hereditary bleeding disorders.

FXIII deficiency attributable to defects in both the FXIIIA and FXIIIB genes has been described. However, a recent review on this bleeding disorder concluded that mutations in the FXIIIA gene are the more common cause of FXIII deficiency.8 This study describes the clinical and genetic features and management of 6 patients with congenital FXIII deficiency. Late diagnosis in 3 of the cases (all related) illustrates the severity of this disorder in the absence of prophylaxis.

MATERIALS AND METHODS

Patients

The 6 patients under study come from 3 unrelated families. All are of Pakistani origin (now residing in West Yorkshire, UK) and the offspring of consanguineous marriages. In the case of 3 children (patients 1, 2, and 3) diagnosis was made in early infancy. However, it was considerably delayed in the case of patients 4, 5, and 6. Additional details are given in “Clinical Features.”

FXIIIA Enzyme-Linked Immunosorbent Assay and FXIII Activity Assay

Plasma FXIIIA levels were determined using an enzyme-linked immunosorbent assay detailed previously.9 Plasma FXIII activity...
was analyzed by measuring the rate of biotinylated pentylamine incorporation into fibrin as described elsewhere.9

DNA Amplification and Sequence Analysis

The gene for FXIIIA is localized to chromosome 6p24–25 and is organized into 15 exons. All 15 FXIIIA exons were amplified by polymerase chain reaction (PCR) and sequenced as described previously.10,11

Computerized Molecular Modeling

The methods and computer programs used to predict the effects of the mutations on FXIIIA polypeptide structure are detailed in Anwar et al.12

RESULTS

Clinical Features

The incidence of intracranial hemorrhage (about 30% of cases) is higher in FXIII deficiency than in any other congenital bleeding disorder and represents a significant threat to early life.13 Patients have a lifelong tendency to bleed into the skin, subcutaneous tissues, and muscles. Bleeding into joints occurs in ~25% of cases and is more commonly peri-articular than intra-articular.8,13 Female FXIII-deficient patients are unable to carry a pregnancy to term and suffer recurrent miscarriage.14,15 An important diagnostic clue for FXIII deficiency is umbilical bleeding in the newborn period, which occurs in about 80% of cases and is almost pathognomonic. Because standard coagulation tests are normal, the diagnosis will be missed unless specific tests are conducted. The screening test for FXIII deficiency is the solubility of the patient’s recalcified plasma clot in urea or monochloroacetic acid.16 A definitive diagnosis is then made on the basis of functional and immunologic assays.

All patients studied had umbilical hemorrhage during the newborn period. Bleeding symptoms experienced by the 6 children are shown in Table 1. It is clear that the 3 patients whose diagnosis, and hence the start of prophylactic treatment, was delayed had significant and serious bleeding manifestations. Diagnosis was made in the neonatal period in the cases of patients 1 and 3, and at 3 months after an intracranial hemorrhage in patient 2. Prophylactic treatment with FXIII concentrate was started after diagnosis, and it is evident that early diagnosis, and hence early prophylactic treatment, virtually abolishes the risk of bleeding. More detailed accounts of the 6 patients are given below.

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Features</th>
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<tr>
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<tr>
<td>Umbilical hemorrhage</td>
</tr>
<tr>
<td>Excessive bruising</td>
</tr>
<tr>
<td>Subcutaneous hematomas</td>
</tr>
<tr>
<td>Excessive bleeding from lacerations</td>
</tr>
<tr>
<td>Oral hemorrhage</td>
</tr>
<tr>
<td>Hemarthrosis</td>
</tr>
<tr>
<td>Epistaxis</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
</tr>
</tbody>
</table>

Patient 1 (Family I)

This boy, a term delivery, had an uneventful neonatal period until he developed bleeding from the umbilical stump at 11 days of age. Platelet count, prothrombin time, activated partial thromboplastin time, serum fibrinogen, and assays of factors VIII, IX, and XI were normal. The urea solubility test was positive. Functional FXIII assay levels ranged from 0.13 IU/mL to 0.32 IU/mL, and immunologic FXIII assay levels ranged from 0.34 IU/mL to 0.41 IU/mL. He has not had any bleeding symptoms since starting prophylaxis with FXIII concentrate.

Patients 2 and 3 (Family II)

Patient 2 had an uneventful neonatal period until he developed umbilical bleeding at the age of 6 days. This stopped after tying the umbilical stump. He was also noted to bleed excessively after circumcision. At the age of 3 months, he presented with vomiting, irritability, drowsiness, and a tense anterior fontanelle. Cranial computed tomographic scan showed a large hematoma in the cerebellar vermis with dilated lateral and third ventricles. Clot solubility in 1% monochloroacetic acid was greatly increased (2 minutes), and FXIII was undetectable. He required a ventriculoperitoneal shunt for hydrocephalus and has been left with a hemiparesis. He has not suffered any additional bleeding problems since starting FXIII prophylaxis.

His sister who was born 5 years later also had umbilical bleeding at the age of 5 days. Her urea clot solubility time was 14 minutes, and the diagnosis was confirmed by FXIII assay. She has not had any bleeding episodes since starting FXIII prophylaxis.

Patients 4, 5, and 6 (Family III)

Patients 4 and 5 are brothers, and patient 6 is their cousin. Patient 4, the eldest member of the family, presented at 10 days with umbilical sepsis accompanied by bleeding. Standard coagulation tests were normal, and his symptoms settled with antibiotics and fresh frozen plasma. He was investigated at the age of 3 years because of a history of excessive bruising and oral bleeding. Prothrombin time, activated partial thromboplastin time, platelet count, and von Willebrand factor screen were normal. Platelet aggregation studies were abnormal. He showed no secondary response to adenosine diphosphate and adrenaline. He had a long lag phase with arachidonic acid and a prolonged lag phase with collagen. Ag-
gregation in response to ristocetin was normal. Platelet nucleotides and platelet membrane glycoproteins were normal. On 2 subsequent occasions, platelet aggregation studies were still abnormal, and a presumptive diagnosis of platelet function abnormality, probably a storage pool disorder, was made. He continued to bruise easily and subsequently had more serious bleeding manifestations with hemorrhage of his right elbow at 7 years old, hemorrhage of his right knee at 10 years old, and an intracranial hemorrhage (from which he fully recovered) at 13 years. These episodes were managed with platelet transfusions.

His brother, who is 4 years younger, also had an umbilical hemorrhage during the neonatal period and a similar history of excessive bruising. He suffered from recurrent epistaxis, excessive bleeding from lacerations, and subcutaneous hematomas after minor trauma. Investigations showed the same abnormal platelet aggregation responses as his brother.

Patient 6, a cousin of patients 4 and 5, had a similar history of umbilical bleeding, excessive bruising, excessive bleeding from lacerations, and subcutaneous hematomas. At the age of 4 years, he had a hemorrhage of his right knee. Investigation showed similar abnormal platelet aggregation results to those of his cousins. FXIII assays were eventually conducted when patients 4, 5, and 6 were aged 14 years, 10 years, and 9 years, respectively. The 2 brothers had FXIII levels of <0.05 IU/mL and their cousin a FXIII level of 0.08 IU/mL. FXIII replacement therapy was then commenced, and patients 4 to 6 have not suffered any additional bleeding episodes.

Management

In the past, whole blood, fresh frozen plasma, cryoprecipitate, or a placental FXIII concentrate have been used in the treatment of FXIII deficiency (reviewed in reference 8). More recently, a plasma-derived pasteurized concentrate has become available for treatment. In view of the very high risk of intracranial bleeding, it has been advocated that all patients with FXIII deficiency should receive prophylactic treatment with FXIII concentrate. The relatively long half-life (11–14 days) of FXIII concentrate makes prophylaxis a simple and practicable procedure. FXIII concentrate given at 4 to 6 weekly intervals has been considerably shown to keep patients free from bleeding symptoms.

All 6 patients now receive FXIII concentrate (Fibrogammin P, Aventis-Behring, Marburg, Germany), which is given at 4 weekly intervals. Fibrogammin P is derived from the plasma of healthy donors. It is negative for hepatitis B surface antigen, anti-hepatitis C virus, anti-human immunodeficiency virus (HIV)-1, and anti-HIV-2. Virus inactivation is conducted by pasteurization (heat treatment in aqueous solution at 60°C for 10 hours). In general, we have aimed to achieve a postinfusion level in the normal range of 0.6 to 1.5 IU/mL and to maintain a preinfusion level of 0.1 IU/mL or more. This level has been considered to be hemostatic. The doses required to achieve this in our patients and the range of preinfusion and postinfusion levels are shown in Table 2. With the exception of patient 2 who received 10 to 20 U/kg every 4 weeks, the other patients have received 30 to 35 U/kg every 4 weeks. Since starting regular 4 weekly prophylaxis, all of the patients have been free of symptoms and none has experienced any side effects from FXIII concentrate. Serology for hepatitis B surface antigen, anti-hepatitis C virus, HIV-1, and HIV-2 has remained negative in all patients.

**Molecular Genetics**

DNA sequence analysis of the FXIII gene in each patient revealed the following sequence changes:

**Family I**

A homozygous GAA→AAA sequence change at codon 102 in FXIII exon 3 of patient 1 (Figs 1A). The parents of patient 1 were each heterozygous for this mutation, providing additional evidence for this sequence change to be disease-causing. This mutation was confirmed to be absent from 200 normal alleles by DNA sequence analysis of FXIII exon 3.

**Family II**

We have reported the molecular basis of FXIII deficiency in this family recently. In summary, patients 2 and 3 carry a homozygous AGC→AGG disease-causing sequence change at codon 295 in FXIII exon 7. The parents in this family were each heterozygous for this mutation.

**Family III**

Interestingly, patients 4, 5, and 6 have the same AGC→AGG sequence change at codon 295 in FXIII exon 7 as that found in Family II (Fig 1B). The parents of patients 4, 5, and 6 were not available for study. We have previously confirmed the absence of this mutation from 210 normal alleles.

There are a number of additional normal DNA polymorphisms in FXIII, which can influence the activities and levels of the enzyme. Interestingly, all the patients shared the same genotypes at all of these loci, with the exception of the −246 G/A FXIII

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### TABLE 2. Clinical Management

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Diagnosis</th>
<th>Age at Start of Prophylaxis</th>
<th>4 Weekly Dose (IU/kg)</th>
<th>Preinfusion Level (IU/mL)</th>
<th>Postinfusion Level (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>First mo</td>
<td>4 y</td>
<td>30</td>
<td>0.22–0.3</td>
<td>0.64–0.85</td>
</tr>
<tr>
<td>2</td>
<td>3 mo</td>
<td>3 mo</td>
<td>10–20</td>
<td>0.15–0.24</td>
<td>0.61</td>
</tr>
<tr>
<td>3</td>
<td>First mo</td>
<td>First mo</td>
<td>25–30</td>
<td>0.13–0.25</td>
<td>0.62</td>
</tr>
<tr>
<td>4</td>
<td>14 y</td>
<td>14 y</td>
<td>33</td>
<td>0.13–0.25</td>
<td>0.45–1.0</td>
</tr>
<tr>
<td>5</td>
<td>10 y</td>
<td>10 y</td>
<td>35</td>
<td>0.13–0.15</td>
<td>0.65–0.8</td>
</tr>
<tr>
<td>6</td>
<td>9 y</td>
<td>9 y</td>
<td>30</td>
<td>0.12–0.12</td>
<td>0.6–1.0</td>
</tr>
</tbody>
</table>

http://www.pediatrics.org/cgi/content/full/109/2/e32
At the −246 locus, patient 1 was G/G homozygous, patients 2 to 5 were A/A homozygous, and patient 6 was G/A heterozygous.

DISCUSSION

Diagnosis and Management

Although rare, FXIII deficiency is an important disorder because of the seriousness of its bleeding manifestations. In particular, the incidence of intracranial hemorrhage is higher than in any other bleeding disorder. Although the majority of cases have severe and at times life-threatening symptoms, there is a spectrum of clinical severity with some recorded cases being detected in adult life as a result of bleeding after minor surgery.

Three of our 6 cases demonstrate how serious the bleeding manifestations can be when diagnosis, and hence prophylactic treatment, are delayed. These 3 individuals, all related, had abnormal platelet function suggesting a possible storage pool defect. With the exception of umbilical hemorrhage, the early symptoms in patients 4, 5, and 6, ie, excessive bruising and oral bleeding, could have been consistent with the diagnosis of a platelet functional disorder. However, they later developed symptoms such as subcutaneous hematomas, periarticular hemorrhage, and intracranial bleeding, which are not in keeping with the abnormalities found in their platelet aggregation studies.

The 3 boys did not have either Glanzmann’s thrombasthenia or Bernard-Soulier syndrome, which are the 2 most serious disorders of platelet function. The remaining disorders of platelet function, including storage pool deficiency, are usually comparatively mild bleeding disorders. Subcutaneous hematomas, joint hemorrhage, and intracranial bleeding are not usual features. Umbilical hemorrhage provides an important diagnostic clue and should lead to a clot solubility test and FXIII assay. It is important to be aware that standard tests for coagulation will fail to detect FXIII deficiency, which must be excluded by specific investigations.

The importance of early diagnosis lies in the fact that serious bleeding manifestations can be completely prevented by prophylactic FXIII concentrate. There are few clotting disorders where prophylaxis is so important and so effective. In view of the high risk of intracranial hemorrhage, it is now recognized that all patients with FXIII deficiency should be offered prophylactic treatment from the time of diagnosis. It has been suggested that FXIII levels of ~3% to 10% of the normal population mean (0.03–0.1 IU/mL) are sufficient to prevent spontaneous hemorrhage. With the exception of patient 1, there was no argument against starting prophylactic treatment in our patients in view of their very low FXIII levels and clinical features. However, patient 1, after having an umbilical hemorrhage in the neonatal period and a positive clot solubility test, was found to have FXIII levels ranging between 0.14 IU/mL and 0.32
IU/mL, levels which at first sight might be considered probably to be hemostatic. After the neonatal period, he had no bleeding symptoms before starting prophylaxis at the age of 4 years. In making our decision to start prophylaxis, we were influenced by the findings of the 1996 European Thrombosis Research Organisation Working Party on FXIII survey of 72 patients. Data relating to clinical symptoms, diagnostic tests, FXIII levels, and management was obtained by questionnaire. In 18 patients, FXIII activity was reported to range from 5% (0.05 IU/mL) to 53% of normal (0.53 IU/mL). In only 3 of these 18 patients was no bleeding reported. Six patients with FXIII levels between 0.1 and 0.4 IU/mL had moderate or severe bleeding manifestations. Although the accuracy of data obtained from different institutions by questionnaire is open to doubt, there was the suggestion that there may not be strict correlation between bleeding symptoms and plasma FXIII levels. This suggestion, together with the possibility of intracranial hemorrhage (patient 1 is a very active boisterous child), persuaded us to commence prophylactic treatment despite his FXIII levels.

The long half-life of FXIII allows prophylactic FXIII concentrate to be given infrequently (at 4–6 weekly intervals). The Fibrogammin P product information suggests 4 weekly intervals although Miloszewski and Losowsky found an interval of 6 weeks to be adequate in the prevention of hemorrhage in 6 adult patients whom they have treated for many years. At the end of 6 weeks, FXIII levels in their patients were between 3% and 5% of normal. On the assumption that young children are more active and more injury prone than adults, we have opted for treatment at 4 weekly intervals and aim to achieve levels of more than 10% of the normal population mean (0.1 IU/mL) at 4 weeks. A level of 10% or more has been suggested to be sufficient to prevent spontaneous hemorrhage. The Fibrogammin P product information suggests a prophylactic dose of 10 U/kg at 4 weekly intervals. Although patient 2 achieved adequate preinfusion levels with 10 to 20 U/kg, our other patients have required around 30 to 35 U/kg.

The dose should be tailored toward plasma levels and clinical efficacy in the individual patient. In common with the experience of others, we have found prophylactic treatment to be completely effective in preventing hemorrhage. None of our patients has had bleeding symptoms since starting prophylaxis. In particular, prophylactic treatment has transformed the lives of patients 4, 5, and 6 who before treatment had frequent and serious bleeding manifestations. None of the 6 patients has experienced any adverse effects from prophylaxis with FXIII concentrate. No allergic reactions have occurred and none has shown evidence of viral transmission.

Molecular Genetics and Molecular Modeling

The GAA→AAA mutation in FXIIIA exon 3 of patient 1 corresponds to a glutamic acid to lysine amino acid change at residue 102, replacing an acidic with a basic residue. In the native protein, residue Glu102 is oriented toward the surface of the β-sandwich domain of FXIIIA (Fig 2A). The side-chain of Glu102 is oriented toward the surface of the protein, and its atoms are involved in a hydrogen-bonding network, which is important in stabilizing this region (Fig 2B). The replacement of Glu102 with lysine produces steric hindrance between atoms of the lysine and the Tyr116 and Arg171 residues (Fig 2C). To accommodate the lysine residue, the side-chains of both Tyr116 and Arg171 would have to move away. However, modeling work shows that this is not possible without resulting in additional steric clashes with other surrounding residues. It seems that the changes required to surrounding residues to accommodate the Lys102 side-chain, are likely to have the effect of destabilizing this whole region. The Lys102 mutant, therefore, is unlikely to fold properly and will probably be less stable than the wild-type molecule.

The AGC→AGG mutation in exon 7 corresponds to a serine to arginine amino acid change at residue 295, in the core domain of the FXIIIA molecule (Fig 2A). Because we have reported the effects of the Ser295Arg mutation on the 3-dimensional structure of the FXIIIA molecule in detail recently, this information will not be repeated here. Briefly, the side-chain of Ser295 is completely buried and tightly packed through specific hydrogen-bond interactions with the side-chains of Thr323 and Trp225. Arginine has a much longer side-chain that cannot be accommodated in the space available. It is, therefore, likely that the mutant Arg295 will again not fold properly, resulting in an unstable molecule.

Molecular modeling of the Glu102Lys and Ser295Arg mutations has suggested adverse effects on stability of these FXIIIA mutant proteins. We are investigating these effects further through the study of recombinant FXIIIA mutant proteins. These data will be published elsewhere.

The presence of a FXIIIA−246G allele has been found to correlate with higher plasma FXIII levels compared with the FXIIIA−246A allele, in the normal population, suggesting that this promoter polymorphism influences the expression of plasma FXIII. As discussed above, the missense mutations identified in patients 1 to 6 are predicted to result in unstable FXIIIA molecules. Plasma FXIII levels, before prophylaxis, would therefore be expected to be very low in patients 1 to 6. The differences observed in the plasma FXIII levels of patients 1 to 6 may partly be explained by the differences in their genotype at the −246 locus. Patient 1 had plasma FXIII levels between 0.34 and 0.41 IU/mL and he is −246G/G homozygous, compared with patients 2 to 6 who had undetectable or <0.05 IU/mL plasma FXIII levels and who are all −246A/A homozygous. Patient 6, who is −246G/A heterozygous, had plasma FXIII levels of 0.08 IU/mL.

The molecular basis for FXIII deficiency is highly heterogeneous. In some cases, the type of mutation a patient carries can influence the severity of bleeding symptoms. For example, Mikkola et al have reported a FXIIIA splicing mutation, which results in abnormal mRNA splicing producing truncated FXIIIA molecules. However, a small amount of cor-
directly spliced \textit{FXIIIA} mRNA, and FXIIIA polypeptide, is also produced. Consequently, the patient suffers from only mild bleeding symptoms. In our study, patients 2 to 6 have very variable clinical features, although they all have the same Ser295Arg disease-causing mutation. Patients 2 to 5 also share the same genotype at all the other known \textit{FXIIIA} polymorphisms. Patient 6 only differs by being heterozygous at the $-/-H_{11002}246G/A$ promoter polymorphism. The variation in severity of bleeding in these patients is clearly not based on their \textit{FXIIIA} genotype alone, but is also dependent on early diagnosis and subsequent prophylaxis, as well as possibly other genetic modifiers on the severity of the bleeding diathesis.

This study illustrates how easy it can be to miss the diagnosis for FXIII deficiency in increasingly busy hospitals, even when the patients are all under the management of the same health authority, as in this case. The benefits of an early diagnosis and implementation of replacement therapy cannot be stressed too highly. The recognition of delayed umbilical bleeding, observed in all our patients, as a presenting feature for FXIII deficiency is imperative and a vital clue for additional specific investigations.

**ACKNOWLEDGMENTS**

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DOI: 10.1542/peds.109.2.e32

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