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Factor XIII deficiency in children--clinical presentation and outcome

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ORIGINAL ARTICLE

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ABSTRACT

Objective: To determine the demographic features and clinical outcome of children with Factor XIII deficiency.
Study Design: Observational case series.
Place and Duration of Study: The Aga Khan University Hospital, Karachi, from January 1996 to December 2006.
Methodology: Records of all hospitalized pediatric patients with discharge diagnosis of FXIII D, on the basis of factor XIII assay 5 mol/L urea test were retrospectively reviewed and abstracted on a pre-specified proforma. Demographic features, coagulation profile, family history and outcomes were noted.
Results: A total of 10 charts were reviewed. There were 5 boys and 5 girls. Almost all the children (9/10) were less than 5 years of age, out of whom 5 (50%) were infants, and 3 were neonates. Bruises and prolonged bleeding after trauma was the major presenting complaints in 80%, followed by prolonged bleeding from the umbilical stump in 2 patients. Nine patients had past history of prolonged umbilical bleeding. Two patients had history of FXIII D in siblings, while 2 had history of prolonged bleeding in other family members (cause unknown). Consanguinity was present in 80% of the families. Initial coagulation screen were normal in all patients. Two patients had intracranial hemorrhage, proved on neuro-imaging, were managed with plasma infusions and required craniotomy. The rest were managed conservatively with plasma transfusions. All were discharged alive in good clinical condition. Almost all were followed regularly in clinic with monthly cryoprecipitate transfusions.
Conclusion: Although factor XIII deficiency is a rare genetic disorder in children with history of bruising, prolonged umbilical bleeding, family history of bleeding and consanguinity with normal initial coagulation screen (PT, APTT and platelets), FXIII D should be ruled out.

Key words: *Factor XIII deficiency. Prolonged umbilical bleeding. Bruising. Consanguinity.*

INTRODUCTION

Congenital Factor XIII deficiency (FXIII D) is a rare genetic bleeding disorder that is inherited in an autosomal recessive pattern with a frequency of 1 per 2 million individuals in the human population.[1] Factor XIII is a pro-enzyme (composed of $2\alpha 2\beta$ subunits), activated to XIIIa by calcium and thrombin in the final step in coagulation cascade.[2] The genes are located on different chromosomes. The locations are as A subunit on 6p25-p24, while B subunit on 1q31-q32.1. Activated factor XIII cross link fibrin and other plasma proteins (most importantly plasmin inhibitor) to not only form a clot and hold it in place but also to ensure that clot will not be digested prematurely.[2] Genetic analysis reveals most cases associated with deficiency of subunit A located on chromosome 6, while a minority is associated with subunit B located on chromosome 1.[3]

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Patients with FXIII D usually present at early neonatal period with prolong umbilical stump bleeding (first and most characteristic symptom), post circumcision bleeding or easy bruises during early days and this type of bleed is fairly common and pathognomic of this disease.[4] Recurrent spontaneous abortions and menorrhagia have also been reported in early pregnancy.[4,5] Typically, bleeding symptoms occur hour or days after trauma.[1] The most threatening and devastating complication with high mortality in these patients is intracranial bleeding.[6,7] The diagnosis can be delayed in FXIII D as the standard coagulation profile is normal in these patients.[4] Being a rare bleeding disorder, it needs a high index of suspicion as transfusion with blood, plasma and other blood products prior to proper investigations can contribute in delayed diagnosis in FXIII D.[7]

Most of the autosomal recessive disorders are associated with consanguinity and that is why the incidence of severe congenital FXIII D is increased in populations where consanguineous marriages are common.[8] Hussain *et al.* reported that 60% of all Pakistani marriages were consanguineous,[9] therefore, the diseases having familial tendency may be associated with higher prevalence than in other

countries.[10] Although congenital deficiency is the commonest, some acquired causes of deficiency may also be seen in other diseases i.e. liver diseases, disseminated intravascular coagulation, and renal insufficiency and with anti-tuberculosis therapy.[11,12]

The objective of this case series was to describe the baseline of demographic and clinical features along with the clinical outcome of 10 pediatric patients with congenital FXIII D, admitted in a tertiary care hospital of Karachi, Pakistan.

METHODOLOGY

It was an observational descriptive case series. The study participants included all patients aged one year to 15 years, who were admitted and discharged from The Aga Khan University Hospital with the discharge diagnosis of FXIII D, from January 1996 till December 2006. Patients were identified by using coded discharge records with the diagnosis of coagulation/factor deficiency, as there is no specific identity available in ICD book. ICD9 CM 286.3 was used for identification of study patients. Diagnosis were confirmed by performing clot solubility tests in 5 mol/L urea, a qualitative test for diagnosis of FXIII deficiency; those found positive were labelled as factor XIII deficient.

Inclusion criteria were cases selected by searching coded discharge records factor XIII deficiency, aged upto 15 years with FXIII D confirmed at the centre. Exclusion criteria were patients with acquired FXIII D.

Data was abstracted on a pre-specified proforma. Features including gender, age at presentation, presenting complaints, family history, consanguinity, and management at hospital, complications and their follow-up visits were recorded. SPSS version 13 was used for data entry and analysis. Mean and standard deviation of age at presentation and hospital stay was calculated, while frequency percentage of gender, consanguinity in parents, family history of bleeding disorder or FXIII D, and complications were recorded.

RESULTS

Ten patients were identified as cases, during the study period, out of 56 patients with bleeding coagulation disorder. Males and females were equal (5 each). Nine patients were less than 5 years (mean age 27 months). Five patients were infants; while 3 were neonates. Easy bruisability and hematoma at different sites were the presenting features to the hospital in 8 patients (Table I). One of them presented with excessive cry, irritability and bulging fontanel, while delayed umbilical stump bleeding was present in 2 patients. Past history revealed that almost all had history of prolonged umbilical bleeding. Five patients had been hospitalized previously with some bleeding complaint. Consanguinity in parents was found in 8 patients. Two patients had history of FXIII D in siblings, while 2 had history of prolonged bleeding of unknown cause in the family. Bruises (7 patients) and pallor (5 patients) were the major clinical findings at presentation. Two patients had intracranial bleeding, proved on neuroimaging, and were managed with fresh frozen plasma, cryoprecipitate, packed red blood cell transfusions and craniotomy. Two patients had large hematoma on body, managed conservatively. Platelets count, and initial coagulation screen (PT, APTT and BT) were found normal in all patients, while a clot solubility tests in 5 mol/L urea test for FXIII deficiency were found to be positive. All the rest were managed with plasma and cryoprecipitate transfusion, while 6 required packed cell transfusion during the hospital stay. All patients were discharged alive (average length of stay 2.6 ± 2.4 days) and followed-up in outpatient clinic. Nine patients were alive and well with no major bleeding episodes at one year of follow-up on prophylactic monthly cryoprecipitate infusion, while one lost the follow-up.

Table I: Demographic features and clinical findings of factor XIII deficient patients.

Characteristics	Patients (n = 10) (%)
Age in months (mean, SD)	27± 20
Neonates	3 (30%)
Infants	5 (50%)
<5 years of age	9 (90%)
Gender	
Males	5 (50%)
Presenting complaint	
Easy bruisability	8 (80%)
Hematoma	8 (80%)
Delayed umbilical bleeding	2 (20%)
Irritability / bulging fontanel	1 (10%)
History of umbilical cord bleeding	10 (100%)
Previous hospitalization	5 (50%)
Consanguineous marriage in parents	8 (80%)
Factor XIII deficiency in family and/or prolonged bleeding history	4 (40%)
Hemoglobin on arrival (mean, SD)	8.4 ±1.6
PT, APTT and BT clinical outcome	Normal
Alive (at discharge)	10 (100%)
Alive (at 1 year follow-up)	9* (90%)
Length of stay (days)	2.6 ± 2.4

**One patient lost to follow-up*

DISCUSSION

Inherited FXIII D is a rare autosomal recessive disorder affecting approximately one out of 1-3 million people.[3] It was first described by Duckert *et al.* in 1960 in a 7-year - old Swiss boy.[13] This disorder is so rare that to-date only 300 patients have been identified.[1] The maximum number of patients were identified in Japan (53 patients).[1] Although a rare disorder because of serious manifestations i.e. intracranial bleeding and recurrent abortions, it has been highlighted more than any other bleeding disorders.[5]

FXIII D has three subtypes.[13] Type I deficiency has both subunit A and subunit B. Type II has no activity of subunit A and reduced to normal activity of subunit B. Type III has normal subunit A and deficiency of subunit B. Literature review showed 2 case series from Pakistani population, one reported 13 while the second reported 6 patients.[10,15] The most common subtype in our country is still not identified, but Anwar *et al.* reported subunit A deficiency as the commonest with different codon mutations in a case series.[15]

Deficiency of factor XIII leads to an unstable clot formation, which is dissolvable in plasma and ultimately leads to bleeding tendency. Most patients in this series presented with bleeding from different sites of body and easy bruisability. Another important feature is prolonged umbilical stump bleeding or delayed cord separation; 2 neonates presented with prolonged umbilical cord bleeding and almost all others had prior history of prolonged umbilical stump bleeding. The findings are comparable with other studies reported in adults showing subcutaneous bleeding (57%), followed with umbilical cord bleeding (56%), muscle hematoma (49%) and intracranial bleeding (34%) to be the major clinical presentation.[16] Most of the patients presented early in their life, which is supported by literature.[1,4,6,15]

Despite the fact that half of the patients sought some medical attention for a bleeding episode prior to presentation, they were not worked up for any bleeding disorder or coagulation abnormality, as this is one of the commonly reported phenomena in the literature.[1,15] Prolonged umbilical bleeding is a hallmark of FXIII D in neonates.[8,17] All the patients had history of prolonged umbilical bleeding, while one had prolonged caput succedaneum, which is also reported in the literature.[18] Any neonate with this complaint should be screened for FXIII D and other bleeding disorders once sepsis has been ruled out, especially, if there is consanguinity or family history of bleeding disorder.

Consanguinity plays a major role in transmission of disease, as in all autosomal recessive disorders, the incidence is more among inter-family marriages. Various case series reported all of their patients being consanguineous and presenting early in life with bleeding diathesis.[1,9,15] Inter-family marriages are fairly common in Pakistan, causing high prevalence of this disease in our country.[9,15] In this study, 8 children had consanguinity in the family. Family history of bleeding disorder and known FXIII D in siblings were not revealed earlier which may have lead to delayed diagnosis. Two patients had family history of some bleeding tendency, while FXIII D was positive in other 2.

Intracranial hemorrhage (ICH) is more associated with FXIII D as compared to other bleeding disorders. ICH may occur spontaneously or after minor trauma and is associated with mortality and morbidity with long-term sequelae. Two patients presented with Intracranial Bleed (ICB) and survived with no neurological sequelae. Association of ICB and mortality is as high as 25%.[12] It is important not only to identify early but also to ensure that these children be started on prophylactic therapy (regular transfusion of plasma or cryoprecipitate or factor XIII concentrate) so as to prevent a very high risk of spontaneous or acquired intracranial bleeding and its consequences.[19] Plasma half-life of factor XIII is long ranging from 5-9 days, thus regular monthly transfusions are required to optimize its level.

Based on our findings, recommendations can be formulated: Children born with a sibling having FXIII D or with family history of bleeding diathesis should be screened. Patient once diagnosed with FXIII D needs to start on prophylactic therapy of regular transfusion of plasma or cryoprecipitate, so serious manifestations i.e. ICH can be prevented. It is also important to perform prenatal screening.

It is also important to develop support groups to increase awareness and help the patients and their families who require regular transfusion of blood and blood products. Currently, a new factor XIII database website (http://f13-database.de) is established having information regarding proteins, mutation and polymorphism of FXIII D. It also provides useful information about demographic situation, diagnosis and treatment possibilities and genotype-phenotype correlation in patients with inherited FXIII D.[16]

CONCLUSION

FXIII D is a rare genetic disorder, but it is seen relatively common in Pakistan because of inter-marriages. Thus, in children with history of bruising, prolonged umbilical bleeding along with any family history of bleeding or easy bruisability and consanguinity in parents, it is essential to rule out FXIII D.

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