Original article

Review of Congenital Factor XIII Deficiency in Single Iraqi Teaching Hospital

Lubna Foad Hussain [1] **,** ***Obeida Amir Abid*** [2]

1 C.A.B.P.(ped) / Specialist Pediatrician,/ Children Welfare Teaching Hospital, Medical City,

2 F.I.B.M.S(Ped) / Specialist Pediatrician, /Children Welfare Teaching Hospital, Medical City,

Received 10/1/2016 revised 24/1/2016 accepted 6/2/2016

Abstract

Background: Factor XIII deficiency is one of the rarest bleeding disorders with an estimated prevalence of 1in 3 million populations worldwide. The main clinical manifestations of the disease are delayed wound healing, recurrent miscarriage, intracranial bleeding, and prolonged umbilical cord bleeding.

Objectives: The aim of this study was to assess the diagnosis and treatment of factor XIII deficiency in Children Welfare teaching hospital in Baghdad.

Patients and Methods: This retrospective study was performed on thirty three patients with the severe factor XIII deficiency. The diagnosis of the disease was done by a wide spectrum of characteristics which is part of inclusion criteria and including family history, clinical manifestations, laboratory tests, clot solubility in 5 M urea or monochloroacetic acid environments.

Results: the common manifestations of the disease at time of diagnosis were bleeding after trauma (42.4%), umbilical cord bleeding (21.2%)and less frequently gum bleeding and ecchymosis.

Conclusions: factor XIII deficiency is a rare disease in Iraq, most patients are diagnosed at the age of 1-10 years, family history was positive in more than half of the patients.

Keywords: congenital Factor XIII deficiency, clot solubility test.

Introduction

Congenital factor XIII (FXIII) deficiency is a rare autosomal recessive disease usually associated with a severe bleeding diathesis [(1)]. The mortality and morbidity are primarily related to bleeding; intracranial hemorrhage can be life threatening. Because the clinical bleeding is severe in most patients with hereditary factor XIII deficiency, the diagnosis is made at an early age, often during infancy. Bleeding from the stump of the umbilical cord within the first days to weeks of life is a characteristic sign that occurs in 80% of affected individuals [(2,3)]. Additional signs of bleeding include the following: CNS hemorrhage is frequent (25-30%) and may occur spontaneously or after minor trauma [(4-7)]. Soft tissue bleeding and bruising are very common [(4,5)]. Hemarthroses occur in 20% of cases .Bleeding that is delayed (ie:12-36h) after trauma or surgery is diagnostic of factor XIII deficiency.[(8)]

FXIII deficiency can be initially diagnosed by observing bleeding episode with normal routine clotting tests including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, platelets count and bleeding time (BT) [(9)].Diagnosis of the disease based on solubility of blood clot in solution of 5 M urea or 2% acetic acid (or1% monochloroacetic acid). These tests are qualitative tests and show positive result if the activity of FXIII in plasma of the patients is absent or close to zero. If the results of test become positive subsequent quantitative analysis of FXIII activity is needed [(10)].

Replacement therapy in this deficiency can be administered through fresh frozen plasma (preferably virus-inactivated), cryoprecipitate and pasteurized FXIII concentrates. The first FXIII from human source that used in replacement therapy was produced from placenta but later this product replaced by plasma extracted FXIII concentrates [(5,11-13)].The aim of the study is to assess the diagnosis and treatment of factor XIII deficiency in Children Welfare Teaching Hospital, Medical City, Baghdad.

Patients and methods

It is a retrospective study. The study participants included all patients age group who were attend the hemophilia center in Children Welfare Teaching

Hospital with the diagnosis of FXIII deficiency, from January 2 000 till April 2015. All patients were identified by using coded discharge records with the diagnosis of factor XIII deficiency. Data collected included: Gender, age at presentation, presenting complaint, family history, type of treatment (fresh frozen plasma, cryoprecipitate), hepatitis B ,C in patients.

The following investigations were reviewed for all patients who presented to the outpatient clinic to establish the diagnosis and included complete blood picture and coagulation screen PT ,APTT and bleeding time which reported to be normal.

Diagnosis was confirmed by performing clot solubility tests in 5 mol/L urea which was done to all our patients, a qualitative test for diagnosis of FXIII deficiency; those found positive were labelled as factor XIII deficient.Results were expressed as frequencies and percentages and presented in tables and figures using Microsoft Office Excel 2013.

Results

Thirty three patients were diagnosed to have factor XIII deficiency. 20(58%) were males shown in Figure (1). The diagnosis of FXIII deficiency was established at 3 age groups; first group less than 1 year, second group 1-10 years and third group more than 10 years; most patients diagnosed at the age of 1-0 years as shown in Figure (2) Post traumatic bruises were the major presenting complaint in 14 patients (42.4%) , followed by prolonged bleeding from umbilical stump in 7 patients(21.2%). One patient had intracranial hemorrhage diagnosed by neuro-imagining study .Table1

Family history was positive in 20 patients (58%).

The products used in the treatment of these patients only when presented with bleeding included fresh frozen plasma, cryoprecipitate. Testing for transmission of viral infections was also done in all our patients and only 2 from 6 patients received plasma were found with hepatitis C positive after repeated transfusions of fresh frozen plasma.

The other 27 patients were treated by cryoprecipitate with no hepatitis C infection .Hepatitis B was found negative in all patients .**Figure3**

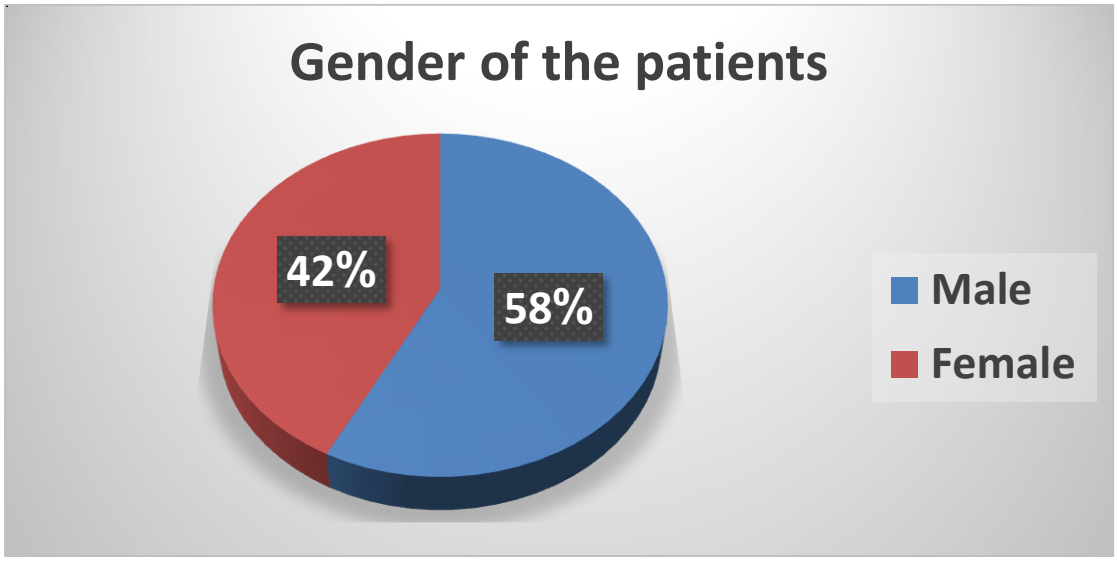

Figure1:The gender of 33 patients

Table1:The presenting complaints at the time of the diagnosis of 33 patients

Bleeding type	Frequency(no.)	Percent(%)
Post traumic bruises	14	42.4
Umbilical cord bleeding	7	21.2
Gum bleeding	5	15.2
After circumcision	2	10% of males
Muscle hematoma	2	6.1
Ecchymosis	1	3.0
Epistaxis	1	3.0
Intracranial hemorrhage	1	3.0
Total	33	

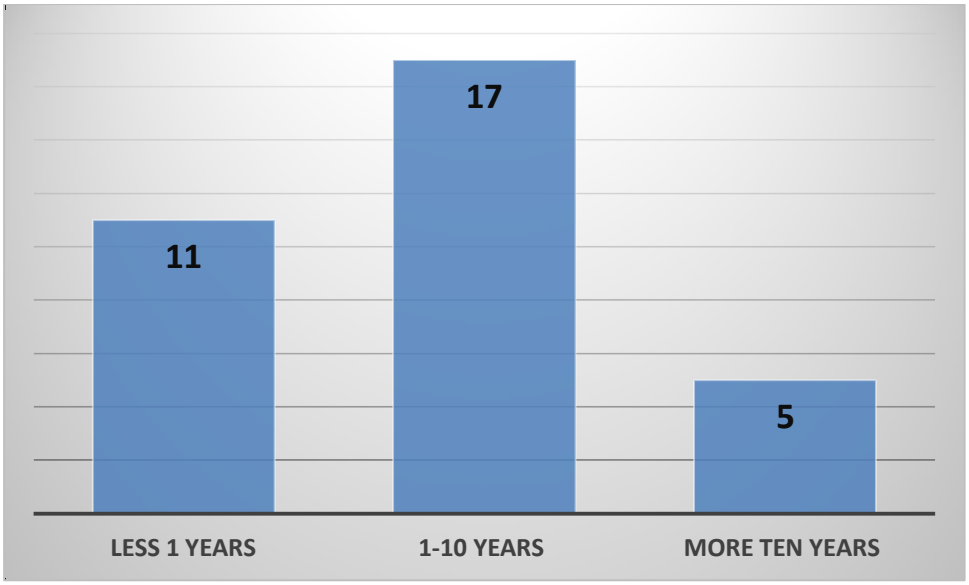

Figure2:The age of diagnosis in 33 patients

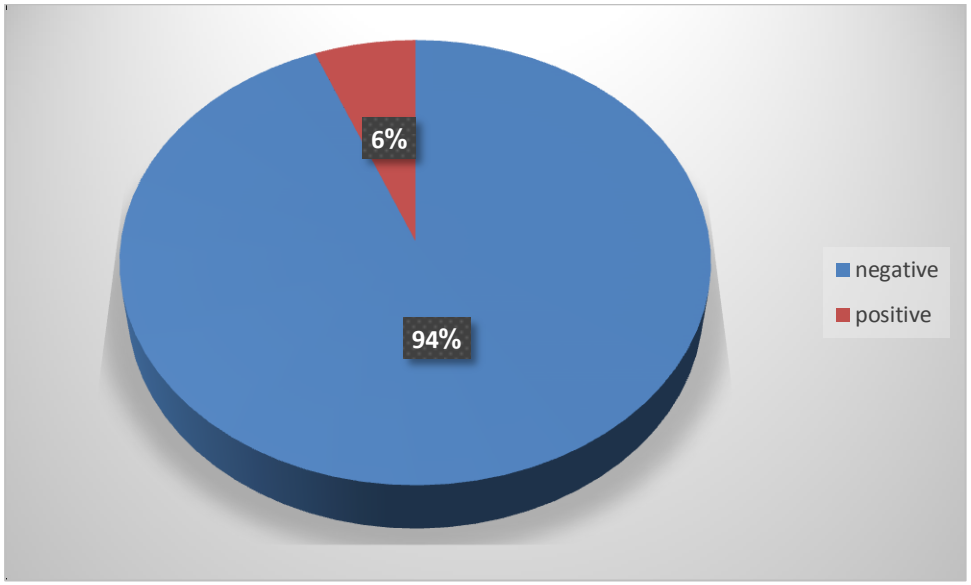

Figure3:The results of Hepatitis C screening

Discussion

This disorder is so rare that to date only 33 of 778 patients with congenital bleeding disorders, have been identified in our hemophilia center with factor XIII deficiency. So the incidence of this disorder is 0.042%. In Saudia Arabia it is also a rare disease [14].While in Pakistan it was the fifth most common factor deficiency detected in one study conducted there [15]. In Iran, a Middle Eastern country with a high rate of consanguineous marriages, there are approximately 473 patients afflicted with FXIII deficiency. An approximately 12-fold higher prevalence of FXIII deficiency is estimated in Iran in comparison with overall worldwide frequency. [14].

In this study, bleeding after trauma is the most common, while in Iranian and Pakistani study showing subcutaneous bleeding (57%), followed by umbilical cord bleeding (56%), muscle hematoma (49%) and intracranial hemorrhage (34%) to be the major clinical presentation [14,15]. In Saudis the presenting symptoms included ecchymosis in 12 patients (71%), bleeding after circumcision in 6 male patients (55%), umbilical stump bleeding in 7 (41%), and intracranial bleeding in 3 patients (18%) [16]. Most of the patients presented early in their life, which is supported by this study which is the same in Iranian, Saudis and Pakistani study.[14-16]

In this study family history is positive in 94% of patients due to higher incidence of interfamilial marriages. In Iranian and Saudi study (59%) had a family history of FXIII deficiency [14,16].In Pakisatan positive family history was present in 42.4% of patients.[15]

In Iraq FXIII concentrate is not available till now, in Pakistan all patients treated with fresh frozen plasma and cryoprecipitate [15] and the same applied for Iran until 2009 when FXIII concentrate became available for patient management. [14]

The challenges that we faced in the diagnosis was the unavailability of quantitative assay and in the treatment was the unavailability of plasma derived FXIII product.

Conclusion

Factor XIII deficiency is a rare disease in Iraq with low incidence, most patients diagnosed at the age of 1-10 years, family history was positive in more than half of the patients.Thus in children with history of post traumatic bruising, prolonged umbilical bleeding along with any family history of easy bruising and consanguinity in parents, it is essential to rule out FXIII deficiency especially in those with normal

Author contributions:

Dr.Lubna Foad Hussain: Acquisition of data analysis , interpretation of data , critical revision.

Dr. Obeida Amir Abid : Study conception, study design, drafting of manuscript, and Coagulation studies.

References

1. Bolton-Maggs PH. The rare inherited coagulation disorders. Pediatr Blood Cancer. 2012: S37.

2. Naderi M, Imani M, Eshghi P, et al. Factor XIII deficiency in Sistan and Baluchistan province. Sci J Blood Transfus Organ. 2013;10(3):282–8

3. Siboni S, Zanon E, Sottilotta G, et al. Central nervous system bleeding in patients with rare bleeding disorders. Haemophilia. 2012;18(1):34–8.

4. Karimi M, Bereczky Z, Cohan N, editors Factor XIIID. Seminars in thrombosis and hemostasis.2009 Jun;35(4):426-38.

5. Eshghi P, Cohan N, Naderi M, et al. Factor XIII deficiency: a review of literature Iranian Journal of Blood and Cancer. 2010;4: 85–91.

6. Sawlani KK, Chaudhary SC, Roy A, et al. Factor XIII deficiency presenting with intracerebral bleed. BMJ Case Rep. ;Epub 2013/01/15.

7. Naderi M, Dorgalaleh A, Alizadeh S, et al. Polymorphism of thrombin-activatable fibrinolysis inhibitor and risk of intracranial haemorrhage in factor XIII deficiency. Haemophilia. 2014 Jan;20(1):e89-92.

8. Helge Dirk Hartung, MD; Chief Editor: Max J Coppes, MD, PhD, MBA.Pediatric Factor XIII Deficiency Clinical Presentation. Medscape.

9. Kessel R, Hu C, Shore-Lesserson L, et al. A child with acquired factor XIII deficiency case report and literature review. 2013 Nov;19(6):814-26.

10. Bay A, Sirikci A, Dogan A, Leblebisatan G, et al. Spontaneous Acute Cerebral Hematoma in a Child with Factor XIII Deficiency. Pediatr Hematol Oncol. 2013.

11. Opat S, Butler J, Malan E, et al. Factor XIII assays. Methods Mol Biol. 2013;992:171–80.

12. Williams M, Will A, Stenmo C, et al. Pharmacokinetics of recombinant factor XIII in young children with congenital FXIII deficiency and comparison with older patients. Haemophilia. 2013.

13. Caudill JSC, Nichols WL, Plumhoff EA, et al. Comparison of coagulation factor XIII content and concentration in cryoprecipitate and fresh-frozen plasma Transfusion. 2009:49(4):765_70.

14. Dorgalaleh A, Naderi M, Hosseini MS, et al.Factor XIII deficiency in Iran: a comprehensive review of the literature.Semin Thromb Hemost . 2015 Apr;41(3):323-9.

15. Anwar M, Iqbal M, Ayyub M ,et al. Prevalence of factor XIII deficiency in patients presenting with a bleeding disorder in Pakistan.Article first published online: DOI: 10.1111/j.1538-7836.2003.0543j.

16. Al-Sharif FZ1, Aljurf MD, Al-Momen AM, et al.Clinical and laboratory features of congenital factor XIII deficiency.Saudi Med J. 2002 May;23(5):552-4.

Correspondence to:

Dr. Obeida Amir Abid

Dept. of hemophilia

Children welfare hospital

Medical city

e-mail: obeida_1968@yahoo.com

Mobile; 07727825155

نقص العامل الوراثي الثالث عشر في احدى مستشفيات العراق التعليميه /دراسه وصفيه

د.لبنى فؤاد حسين1 د.عبيده عامر عبد2

1,2 طبيب اختصاص في طب الاطفال/ مستشفى حماية الاطفال التعليمي/ مدينة الطب

الخلاصه:

خلفية البحث: نقص عامل التخثر الثالث عشرالوراثي هو من الاضطرابات النزفيه النادره التي تحدث في البشر, تقدر نسبة حدوثه بنسبة 1 لكل 3 مليون من عامة الناس.من اهم علامات المرض تأخر التئام الجروح, اسقاطات متكرره عند الحوامل, نزف مطول من مكان الحبل السري عند حديثي الولاده.

الاهداف : تهدف هذه الدراسه الى تحديد عوامل التشخيص والعلاج لنقص عامل التخثر الثالث عشر النزفي الوراثي في مستشفى حماية الاطفال التعليمي في بغداد.

المواد والطرق: دراسه مسترده ووصفيه ل33 مريض مشخصين بنقص عامل التخثرالثالث عشر الوراثي اجريت بين الاول من تموز2000 الى الاول من ابريل 2015. تم التشخيص بالاعتماد على التاريخ العائلي والعلامات السريريه والفحوصات المختبريه.

النتائج: اكثر العلامات المرضيه شيوعا عند المرضى اثناء التشخيص كانت النزف بعد حدوث الاصابات ,النزف من مكان الحبل السري عند حدبثي الولاده, نزف اللثه ثم ظهور بقع نزفيه تحت الجلد.

الاستنتاج: تظهر هذه الدراسه ان نقص عامل التخثر الثالث عشر الوراثي هو من الامراض النادره في العراق .اكثر الاعمار التي يتم فيها تشخيص المرض 1 -10 سنوات. تاريخ العائله كان موجبا في اكثر من نصف الحالات المرضيه.

الكلمات الرئيسية: نقص عامل التخثر الثالث عشر الوراثي, نزف مطول من مكان الحبل السري, اختبار ذوبان الجلطه.