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A retrospective study on clinical manifestations of neonates with FXIII-A deficiency

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ABSTRACT

We assessed clinical presentations and the rate of central nervous system (CNS) bleeding in neonates with FXIIID who exhibited bleeding diathesis in the early days of their lives. A total of 27 neonates presented bleeding or abnormal clinical symptoms, diagnosed with FXIII deficiency were evaluated. Factor XIII concentrate was initiated as the first-line of treatment, and prophylactic therapy was given to all patients. Umbilical cord bleeding, delayed detachment of umbilical stunt, seizure, hematoma, and ecchymosis were concurrent complications in 27 (100%), 5 (18.5%), 5 (18.5%), 3 (11.1%), and 1 (3.7%) of the patients, respectively. History of having CNS bleeding was detected in 13 (48.1%) patients. There was no significant association between CNS bleeding and gender, familial history of FXIIID, or other clinical presentations. Also, there was no significant difference in the mean age of the patients who had CNS bleeding (3.4 ± 0.9 days) and without CNS bleeding (2.9 ± 0.7 days). However, a near significant threshold difference between the patients with and without CNS bleeding was found regarding the mean number of suspicious FXIIID death in their family (1.8 ± 0.5 and 0.7 ± 0.1, respectively, $P = 0.05$). Therefore, a suggested diagnostic algorithm based on prenatal diagnosis could be useful for timely detection of FXIII deficiency in neonates.

1. Introduction

Congenital bleeding disorders should be considered in children with bleeding tendency. Inherited deficiencies of coagulation factors, except FVIII and FIX, are collectively known as rare bleeding disorders (RBDs) [1]. Bleeding severity varies in RBDs, even in the same rare coagulation deficiency and in the same patient over a different period of life [2]. This necessitates physicians and other care providers to become familiar with these variables.

FXIII is a tetrameric protein, consisting of A and B subunits (A_2B_2 structure). Although FXIII deficiency (FXIIID) can be caused by both subunit deficiencies, the most common pattern is subunit A deficiency comprises 95% of FXIIID cases [3]. Subunit A is generated within megakaryocytes, monocytes and placenta by a gene encoding on chromosome 6 (*F13A1*). Recently, it was stated that resident macrophages are the major source of FXIII-A in the plasma. In addition, placenta contains a high amount of FXIII-A, which is produced by placental macrophages [4]. Moreover, the liver is the sole producer of B subunit, expressed by its specific gene on chromosome 1 (*F13B*) [5]. In Iran, FXIIID is estimated to be 12-times more prevalent in comparison to other regions (1 in 2 million individuals) of the world [3]. The rate of FXIIID is even higher in developing countries as diagnostic equipment are inaccessible. In addition, many of the patients with FXIIID might die due to intracranial hemorrhage (ICH) at early age before any definite diagnosis could be made [6–9]. With current diagnostic and care management protocol, the death rate amongst Iranian patients with FXIIID has reached about 15.4% in various stages of life. Umbilical bleeding presentation, ICH, petechiae, purpura, ecchymosis, hematoma

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and join bleeding are the main manifestations of FXIIID in neonates [10].

To the best of our knowledge, there is no study on the clinical aspects and ICH rate amongst neonates with FXIII-A deficiency. On the other hand, the most common cause of mortality and morbidity between FXIIID patients is CNS bleeding; hence, we aimed to determine the frequency and possible risk factors of neonates diagnosed with FXIII-A deficiency in Iran. Also, positive family history and availability of prenatal diagnosis led us to draw a proposed diagnostic algorithm for early detection of FXIII deficiency in neonates.

2. Materials and methods

2.1. Subjects

This cross-sectional and retrospective study was carried out from March 2010 till March 2015 in southeastern Iran. A total of 27 neonates with bleeding events early in life and diagnosed with FXIII-A deficiency were evaluated. In Iran, the diagnosis of FXIIID is based on both qualitative (Clot solubility test using two methods, 5Molar urea and monochloroacetic acid assay) and quantitative (The ammonia release assay using Berichrom® FXIII, Dade-Behring, Marburg, Germany and Technochrom® FXIII, Technoclone, Vienna, Austria) as well as molecular analysis [7]. All clinical and demographic data including; age, gender, type of bleeding, the familial history of abortions, history of CNS bleeding, number of suspicious FXIII-A deficient deaths in the family, family history of FXIIID and types of imaging were recorded in a researcher designed questionnaire. Suspicious death refers to neonatal death due to bleeding events, such as ICH with no definite diagnosis in the known affected family with FXIIID. Plasma derived factor XIII concentrate (Fibrogammin, CSL Behring, Germany) with a dose of 10–30 IU/kg was initiated as the first-line of treatment in the affected neonates. A second dose of therapy was also administrated 2 days later, and then prophylactic therapy of FXIII concentrate was commenced every 28 days with a low dose of 10 IU/kg. The informed consent was obtained from their parents or legal guardians, and the study was approved by the local Ethics Committee.

2.2. Statistical analysis

Data were analyzed using the statistical package for the social sciences (SPSS) software version 19 (SPSS Inc., Chicago, IL, USA). Descriptive data were presented as mean, standard deviation and percentages. Comparison of qualitative variables between the two groups of patients with and without CNS bleeding was done, using Fisher exact test. Quantitative variables were compared by Student *t*-test between the two groups. A P value < 0.05 was considered to be statistically significant.

3. Results

Out of 27 neonates, 14 (51.9%) were females. The mean age of the patients was 6.4 ± 3.1 days (minimum of 3 and maximum of 13 days). Table 1 shows the clinical and demographic data of all included neonates. The first dose of FXIII concentrate was commenced immediately following the first bleeding event. All the neonates were on low dose prophylaxis regimen without further life-threatening bleeding. Umbilical cord bleeding (UCB) was recorded in all patients, and also UCB was the only presentation in 13 (48.1%). A delayed detachment of umbilical stump, seizure, hematoma, and ecchymosis were concurrent complications with UCB in 5 (18.5%), 5 (18.5%), 3 (11.1%), and 1 (3.7%) of the patients, respectively. The family history of FXIII-A deficiency, and the suspicious deaths due to FXIIID in the family were observed in 18 (66.7%), and 19 (70.3%), respectively. Trp187Arg (exon 4, C.559T > C) mutation was the only FXIIID mutation, found in all patients.

History of CNS bleeding was detected in 13 (48.1%) patients, confirmed by sonography or CT-scan. There was no significant association between CNS bleeding history and gender, familial history of FXIIID, or clinical presentations ($P > 0.05$). Also, there was no significant difference in the mean age of patients with CNS bleeding (3.4 ± 0.9 days) and without CNS bleeding (2.9 ± 0.7 days) ($P > 0.05$). However, a borderline significant threshold difference between the patients with and without CNS bleeding was found regarding the mean number of suspicious FXIIID death in the family (1.8 ± 0.5 and 0.7 ± 0.1, respectively, $P = 0.05$). From all the affected patients, 20 (74%) were delivered via normal vaginal delivery (NVD) and 7 (26%) through cesarean section (CS). Nine out of 20 patients with NVD (45%) experienced CNS bleeding and 11 patients (55%) had no history of CNS bleeding. Also, 4 patients with CS (57.1%) experienced CNS bleeding and 3 patients (42.9%) had no history of CNS bleeding. There was no statistically significant difference between the type of delivery (NVD vs. SC) and its relation with CNS bleeding ($P = 0.677$).

4. Discussion

Clinical manifestations of FXIIID encompass wide-variety of bleeding symptoms. These can be either spontaneous or provoked bleeds after trauma, surgery, dental operation, etc. In line with appropriate diagnostic laboratory tests, clinical and familial history can be used to assist the diagnostic process. In the present study, characterizing UCB, along with a variety of other features were observed in neonates who were diagnosed with FXIII-A deficiency. ICH was observed in 48.1% of the patients, while familial history was positive in 66.6%. Emphases on timely diagnosis in suspected cases are essential to reduce morbidity and mortality. Also, type of delivery may trigger bleeding symptoms such as CNS bleeding in the affected patients. CS might be superior to NVD, if fetus is affected with FXIIID, but the mother's coagulation status has to be taken into consideration [11]. In this study, there was no statistically significant difference between the type of delivery and CNS bleeding which might be due to low number of included subjects. However, manipulated or complicated NVD using forceps or vacuum would be associated with higher risk of CNS bleeding compared to CS in rare coagulation disorders.

Despite being the country with the most prevalence of FXIIID around the world, studies on neonates with FXIIID and their clinical presentations are scare in Iran. The most common clinical feature amongst Iranian patients with FXIIID is UCB followed by ICH, and hematoma, which was reported amongst neonates in the present study [12]. However, bleedings that has the highest impact on the lives of patients, are CNS bleeding that incur a high rate of mortality and morbidity. Nearly 30% of patients suffering from FXIIID may experience hemorrhaging episodes in the brain that can be encountered at any stage of life in the affected patients. Our study can be a guide for physicians and neonatal nursing care. Detecting positive family history led us to be highly suspicious and consider prenatal diagnosis (PND), if accessible. Positive PND renders preferred CS over NVD, which prevents further complications. In this study, all the patients were treated with factor XIII concentrates on the first presentation and it was repeated two days later, and thereafter prophylactic therapy was initiated at a low dose of 10 IU/kg every 4 weeks, leading to an acceptable result. As we performed in our patients, continuous factor replacement therapy is the primary therapeutic approach in patients with severe factor XIIID [13]. The relatively long half-life of administrated FXIII concentrates (7–14 days) allows prophylactic factor replacement strategy to be successfully implemented in deficient patients. However, the life-span of infused FXIII is also dependent on both dose and frequency of administrated concentration [14]. In this study, after initial clinical evaluation, we performed general first-line coagulation tests followed by a molecular diagnostic assay. The first line coagulation tests including; PT, APTT, BT, fibrinogen assay, and platelet count were within normal rage in these patients. However, definite diagnosis, using specific factor

Table 1
Demographical and clinical features of 27 neonates presenting with bleeding complications.

	Age (days)	Sex	Presenting symptoms	Familial history of FXIIID	Number of suspicious FXIIID deaths in family	History of CNS bleeding	Type of delivery	Imaging study
1	4	M	UCB + hematoma	+	1	+	NVD	SONO + CT scan
2	3	M	UCB + seizure	+	1	+	NVD	SONO + CT scan
3	10	F	UCB + delayed umbilical stunt detachment	+	3	+	NVD	SONO + CT scan
4	3	F	UCB + seizure	+	2	+	NVD	SONO + CT scan
5	5	F	UCB + hematoma	+	0	−	NVD	SONO
6	13	F	UCB	+	0	−	NVD	SONO
7	4	M	UCB	−	1	+	CS	SONO + CT scan
8	3	F	UCB	−	1	+	CS	SONO + CT scan
9	10	M	UCB + delayed umbilical stunt detachment	+	2	−	NVD	SONO
10	7	F	UCB	−	1	−	CS	SONO
11	5	F	UCB	−	0	−	NVD	SONO
12	7	M	UCB	+	1	−	NVD	SONO
13	10	F	UCB + seizure	+	1	+	NVD	SONO + CT scan
14	4	F	UCB + seizure	+	1	−	CS	SONO
15	5	M	UCB + seizure	−	2	−	NVD	SONO
16	13	F	UCB + delayed umbilical stunt detachment	−	5	+	CS	SONO + CT scan
17	10	M	UCB	+	1	+	NVD	SONO + CT scan
18	6	M	UCB + hematoma	+	0	−	NVD	SONO
19	3	M	UCB	−	0	−	NVD	SONO
20	4	F	UCB	−	1	−	NVD	SONO
21	5	M	UCB + ecchymosis	−	1	+	NVD	SONO + CT scan
22	4	F	UCB	+	6	+	CS	SONO + CT scan
23	5	F	UCB	+	0	−	CS	SONO
24	6	M	UCB	+	0	+	NVD	SONO + CT scan
25	8	M	UCB + delayed umbilical stunt detachment	+	0	+	NVD	SONO + CT scan
26	7	F	UCB	+	1	−	NVD	SONO
27	10	M	UCB + delayed umbilical stunt detachment	+	1	−	NVD	SONO

Abbreviations: CNS; central nervous system, UCB; umbilical cord bleeding, SONO; sonography, CT; computed tomography, FXIIID; FXIII deficiency.
All the patients received FXIII concentrate as a therapy.
The FXIII-A deficient mutation type in all patients was Trp187Arg.

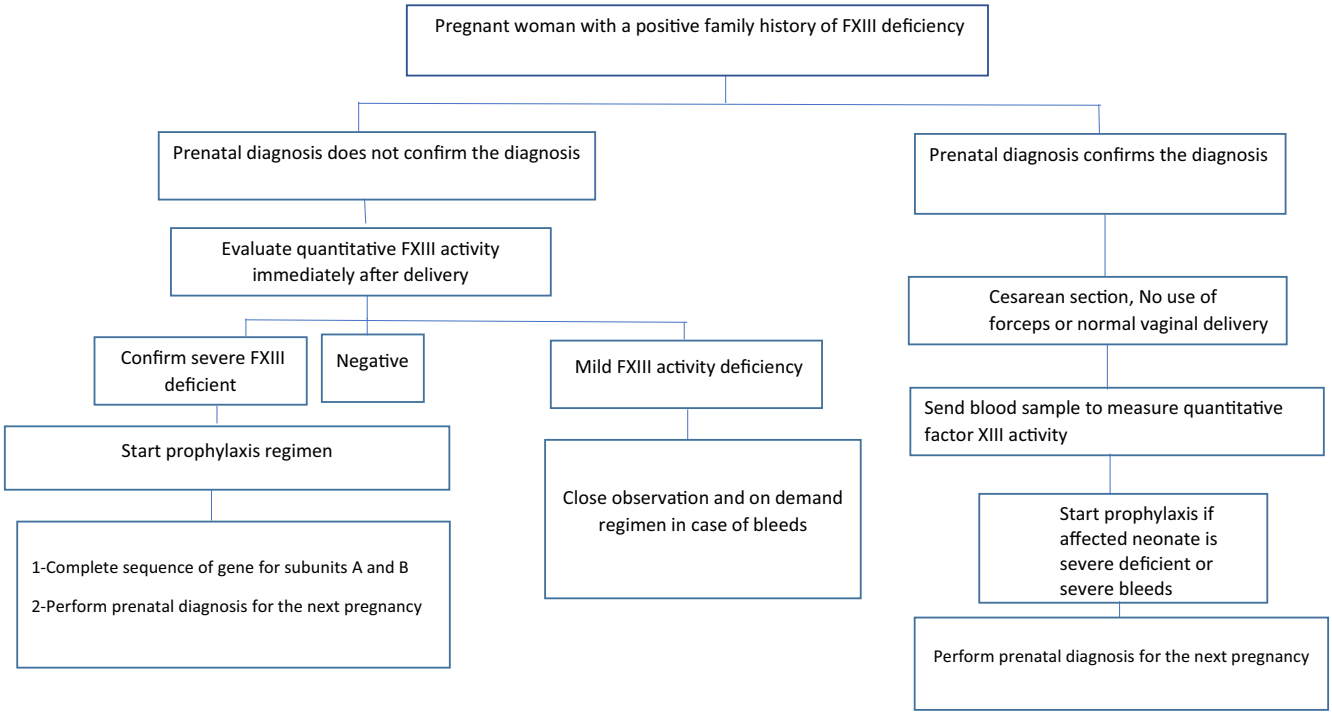

Fig. 1. A proposed diagnostic algorithm for detection of neonatal FXIII deficiency based on prenatal diagnosis.

assay (functional or antigenic level assessment, as well as clot solubility test) are required since negative molecular screening test cannot rule out FXIIID [15]. On the other hand, clot solubility test is no longer recommended due to lack of specificity. More than 150 mutations reported to be responsible for FXIIID worldwide. Amongst these, Trp187Arg (exon 4, C.559T > C) mutation is the most common, and the only reported mutation in southeastern Iran [16,17]. In Iran, molecular diagnostic approach for detecting RBDs is not routine due to limited resources. This approach is mainly confined to prenatal diagnosis centers, especially our center, which provides screening programs for parents.

5. Conclusion

In conclusion relatively high rate of ICH in neonates with FXIIID necessitates early consideration for appropriate detection and timely therapy. Positive family history of FXIIID and availability of prenatal diagnosis leads to a proposed diagnostic algorithm for early detection and timely management of affected neonates with FXIII deficiency (Fig. 1).

Declaration of interests

The authors report no conflicts of interest.

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