Original Article

Bleeding Episodes among Patients with Congenital Fibrinogen Disorders, a Study on 12 New Iranian Patients

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Abstract

Background: Congenital fibrinogen disorders (CFDs) comprise about 10% of rare bleeding disorders (RBDs). CFDs are divided into two groups of quantitative (afibrinogenemia and hypofibrinogenemia) with autosomal recessive inheritance pattern, and qualitative (dysfibrinogenemia, hypodysfibrogenemia) disorders, mainly with autosomal dominant inheritance pattern. Sistan and Baluchestan Province in Iran, with its high rate of consanguineous marriages, has a high incidence of RBDs including CFD. In the current study, we report clinical manifestations of patients with CFDs.

Materials and Methods: Twelve new Iranian patients from Sistan and Baluchestan province with different types of CFDs were selected for this study. Diagnosis of CFDs was based on clinical features and familial history followed by laboratory assessment by routine and specific coagulation tests including prothrombin time (PT) and activated partial time tests (APTT), as well as FI activity assay by Clauss method.

Results: Out of 12 patients, 3 (25%) had afibrinogenemia, and 7 (58.3%) had hypofibrinogenemia, while 2 (16/7%) were suspected of having dysfibrinogenemia. Although umbilical cord bleeding (UCB) 9 (75%) was the most common clinical presentation among the study population, this feature was not observed among patients with dysfibrinogenemia. Hematoma (100%) was the most common presentation of patients with dysfibrinogenemia.

Conclusion: Results of this study revealed that some clinical presentations are the diagnostic features of CFDs and can be used for precise and in-time diagnosis CFDs in conjunction with family history and laboratory findings.

Keywords: Congenital fibrinogen deficiency, Rare bleeding disorders, Afibrinogenemia

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Introduction

Fibrinogen, or coagulation factor I (FI), is one of the acute-phase proteins that increases in response to stress and injury and is mainly secreted by hepatocytes as a 340 KDa glycoprotein. Plasma level of fibrinogen is 160-400 mg/dL with half time of about 4 days (1, 2). Fibrinogen is a hexamer glycoprotein linked by 29 disulfide bonds; it is an asymmetric molecule with identical heterotrimers that, on each

side, consist of three chains including A (FGA), B (FGB) and γ (FGG) chains (3). Each of these chains is encoded by a separate gene with a length of 50 kbp on chromosome 4 (3, 4). Structurally, fibrinogen has a central domain (E) that encompasses the N-terminal of fibrinogen chains and connects to the peripheral domain (D) which contains the C-terminal of β and γ chains (5).

Congenital fibrinogen disorders (CFD) are a group of coagulation disorders based on plasma fibrinogen level, divided into two types of quantitative, or type I, deficiencies including afibrinogenemia and hypofibrinogenemia, and qualitative, or type II, including dysfibrinogenemia and hypodysfibrinogenemia (3, 6). Afibrinogenemia is a rare bleeding disorder (RBD) with a variable bleeding tendency from mild to severe, life-threatening bleeding episodes (7, 8, 9). Patients with hypofibrinogenemia have a similar bleeding pattern, but their bleeding diatheses have a milder course (10). Type II fibrinogen deficiencies have variable bleeding tendency. In contrast to quantitative fibrinogen disorders, however, a considerable number of patients have thrombotic events. In spite of hypofibrinogenemia and afibrionogenemia, the amount of fibrinogen is normal in type II, whereas the function of fibrinogen antigen is reduced (11). CFDs are inherited mainly in autosomal recessive manner and therefore are more frequent in areas with a high rate of consanguineous marriage. Iran's high rate of consanguineous marriage results in a high rate of autosomal recessive disorders, including RBDs (3). In the current study, we report the clinical presentations of 12 new Iranian patients with CFD.

Methods

This study was conducted on 12 patients with CFD. All patients were selected from the Hemophilia Center of Zahedan. Initially, consent was obtained from all the participants and the study was approved by the medical ethics committee of Tehran University of Medical Science. At the beginning of the study, all patients were examined by a physician with expertise in bleeding disorders and all were interviewed by expert staff to complete a questionnaire that contains a number of questions about gender, age, race, as well as type and duration of treatment, therapeutic response, clinical manifestations and complications of treatment.

All patients suspected of CFD were referred to the coagulation laboratory of the Iranian Blood Transfusion Organization (IBTO) of Zahedan for routine and specific coagulation tests. All patients were evaluated by routine coagulation tests including prothrombin time (PT) (normal range: 10.5-12.2 seconds), activated partial thrombin time (APTT) (normal range: 24-38 seconds), thrombin time (TT), reptilase time (RT) (normal range:15-18 seconds, and 19-21 seconds, respectively) (STA Compact automated coagulometer (Stago, Paris, France), bleeding time (BT) (normal range:3-8 minutes) (based on Ivy method), and platelet count (normal range:150,000- 450,000) (Sysmex Kx-21 Haematology Analyzer, Kobe, Japan). Patients with prolonged PT, PTT, TT and/or RT were candidate for fibrinogen assay by the Clauss method (normal range: 160-400 mg/dL). Finally, results were reported as mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables.

Results

The study population included 6 (50%) women and 6 (50%) men; the mean age of the patients and the mean age of diagnosis were 13.2±4 and 4.2±2 years old, respectively. Out of 12 patients, 7 (58%) were born into a consanguineous marriage. Routine coagulation tests including PT, PTT and TT were increased in afibrinogenemia and hypofibrinogenemia patients while in patients suspected of dysfibrinogenemia these assays were relatively increased.

Three patients (25%) had afibrinogenemia, 7 (58.3%) had hypofibrinogenemia while 2 patients (16.7%) were suspected to have dysfibrinogenemia, based on clinical features and laboratory assays. The mean level of functional fibrinogen activity in afibrinogenemia and hypofibrinogenemia patients was <10mg/dl and 18mg/dl respectively while in patients suspected of dysfibrinogenemia the mean level of fibrinogen activity was 109.5mg/dl (Table 1).

Umbilical cord bleeding was the most common presentation leading to CFD diagnosis in all patients with afibrinogenemia; it occurred in 6 patients (85.7%)

Table 1: Frequency of Congenital Fibrinogen Disorders in Study Patients

Congenital fibrinogen disorders	Percentage of disorders	Functional fibrinogen	UCB*	Hematoma	Miscarriage
Afibrinogenemia	25%	<10 mg/dl	100%	_	_
Hypofibrinogenemia	58/3%	<18 mg/dl	85/7%	14/2%	14/2%
Dysfibrinogenemia	16/7%	109/5 mg/dl	_	100%	_

*UCB: Umbilical Cord Bleeding

Table 2: Congenital Fibrinogen Disorders in a Province of Iran, Italy and Worldwide

Factor	I	II	V	V-VIII	VII	X	XI	XIII
Worldwide	10	2	10	3	23	9	37	6
Italy	8	5	10	9	25	8	24	11
Sistan& Baluchestan*	3.1	2	5.8	0.3	6.2	2.8	0.3	79.5

*According to total number of 292 patients with RBD in the province.

with hypofibrinogenemia. Hematoma was seen in all patients with dysfibrinogenemia while observed in only one patient with hypofibrinogenemia. Miscarriage was observed in only one patient with hypofibrinogenemia (Table 1).

Discussion

Sistan and Baluchestan Province, in the southeast of Iran, has high rate of RBDs, specifically factor XIII (FXIII) deficiency. The estimated incidence of afibrinogenemia, the most severe form of CFD, is one per one million in the general population, while the prevalence of other CFDs is higher. In southeast Iran, with a population of 2,700,000, 12 patients were diagnosed with CFDs. According to our last survey in 2011, CFDs comprise 3.1% of all RBDs in southeast Iran (Table 2) (12).

Out of 12 patients with CFDs, 3, 7, and 2 patients had afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia respectively, therefore the incidence of CFDs is higher in southeast of Iran compared to the general worldwide prevalence of this disorder. Afibrinogenemia is the most severe form of CFDs and, in the current study, umbilical cord bleeding was the first clinical finding among all three patients with afibrinogenemia. According to the study by Peyvandi et al, umbilical cord bleeding is a grade III (life-threatening) bleeding that requires immediate medical intervention. Umbilical cord bleeding is the most common clinical presentation among patients with FXIII deficiency (FXIIID). Our recent study on a large number of FXIIID patients found that umbilical cord bleeding is one of their most common causes of death. Therefore, in areas such as Sistan and Baluchestan Province, with high rates of RBDs, umbilical cord bleeding should be considered diagnostic of FXIIID and afibrinogenemia, requiring immediate medical intervention. It previously was reported that patients with hypofibrinogenemia had milder presentations, but among our patients, umbilical cord bleeding was the most common presentation, seen among all seven patients (85.7%). Severe clinical presentations such as menorrhagia (40%) and hematoma (12%) were seen among patients with hypofibrinogenemia in other studies but in current study their presentations were more severe than usually reported (10). Patients with inherited dysfibrinogenemia are usually asymptomatic; nonetheless bleeding diathesis, thromboembolic complications, or both, were seen in these patients (11). Clinical presentations of patients with dysfibrinogenemia were severe, most common among them being hematoma. Although thrombotic diathesis can be observed among patients with CFDs, especially dysfibrinogenemia, none of our patients experienced

this diathesis.

It seems, therefore, that clinical features can be used as diagnostic clues for precise and in-time diagnosis of CFDs, especially umbilical cord bleeding, which was the first clinical finding in 9 (75%) of our patients.

Conclusion

Results of this study revealed that some clinical presentations are the diagnostic features of CFDs and can be used for precise and in-time diagnosis CFDs in conjunction with family history and laboratory findings.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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