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Congenital fibrinogen deficiency in Hemophilia Center Medical City/ Baghdad

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Abstract:

CONTEXT: Congenital fibrinogen deficiency is a rare inherited coagulation disorder with an estimated prevalence of 1:1,000,000 which is characterized by bleeding that varies from mild to severe and by an extremely low level or complete absence of plasma and platelet fibrinogen.

AIMS: This study aims to assess prevalence, demographic parameters, clinical presentation, and hemostatic values in patients diagnosed with congenital fibrinogen deficiency.

SETTINGS AND DESIGN: A retrospective descriptive study of patients diagnosed with congenital fibrinogen deficiency in Hemophilia Center/Medical City/Baghdad over a period of 7 years (from August 2008 to August 2015).

SUBJECTS AND METHODS: The study included patients diagnosed with congenital fibrinogen deficiency. The confirmation of diagnosis was done based on a low fibrinogen assay. All the fibrinogen deficient patients were diagnosed on basis of having fibrinogen level (<150 mg/dl).

RESULTS: There were 111 cases of other coagulation factors deficiency (rare bleeding disorders) registered in the center, congenital fibrinogen deficiency represented 25 (22.5%) of them. Out of 25 patients with congenital fibrinogen deficiency, 8 patients (32%) had fibrinogen level <20 mg/dl (afibrinogenemia) and 17 patients (68%) had fibrinogen level between (20 and 150 mg/dl) (hypofibrinogenemia). The males were 17 patients (68%) and females were 8 patients (32%). The consanguinity was present in 16 (64%) and 11 patients (44%) who had a positive family history of the diseases. The patients with afibrinogenemia mostly presented with hemarthrosis (22.7%) while patients with hypofibrinogenemia mostly presented with menorrhagia (50.0%). The patients who were their symptoms manifested before the 1st year of their age most frequently developed life-threatening bleeding (central nervous system and gastrointestinal bleeding) which were observed in 4 cases. Most of the patients included in this study were without complications (80%) while just one patient (4%) died due to gastrointestinal bleeding others were complicated with viral hepatitis, hepatitis B in one patient (4%) and 3 patients (12%) developed hepatitis C.

CONCLUSIONS: Congenital fibrinogen deficiency founded to be one of the most frequent rare bleeding disorders among Iraqi patients, with a high rate of consanguineous marriage and positive family history. There was a high frequency of life-threatening bleeding among patients who develop symptoms before the 1st year of their age, without notable major complications among the majority of patients.

Keywords:

Clinical presentation of congenital fibrinogen deficiency, congenital fibrinogen deficiency, prevalence of congenital fibrinogen deficiency

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Introduction

Congenital hypofibrinogenemia/afibrinogenemia disorder (CFDs) is a rare inherited coagulation disorder characterized by bleeding that varies from mild to severe and by an extremely low level or complete absence of plasma and platelet fibrinogen.[1] Monoallelic or biallelic mutation of chromosome 4 in fibrogen alpha-chain gene, fibrinogen gamma, and fibrinogen beta genes are responsible for CFDs. The classification of CFDs is based on the level and function of fibrinogen, a quantitative disorders include a complete deficiency of fibrinogen (afibrinogenemia) and decrease level of antigenic fibrinogen (hypofibrinogenemia), and qualitative disorders which include normal level of fibrinogen with decreased function (dysfibrinogenemia) and decrease level and function of fibrinogen (hypodysfibrinogenemia).[2] The primary physiological role of fibrinogen is in hemostasis. In the final step of the coagulation cascade, fibrinogen is converted to fibrin, with formation of a fibrin clot. The first step in this conversion is thrombin cleavage of fibrinopeptides A and B from the fibrinogen α and β chains; the residual molecule is referred to as fibrin monomer. A loose fibrin clot develops as fibrin monomers spontaneously polymerize. The formation of a firm insoluble fibrin gel depends on cross-linking of the polymer by the transglutaminase activity of factor XIIIa.[3] Fibrinogen half-life is 3–4 days and it is also able to bind several cytokines in particular vascular endothelial growth factor, fibroblast growth factor-2, and interleukin-1 (IL-1) β. This is postulated to concentrate the factors at the site of vascular injury and promote wound healing.[4] Although the primary function of fibrinogen is in fibrin clot formation, it has a multitude of other functions, including nonsubstrate thrombin binding, platelet aggregation, and fibrinolysis. Exposure of its nonsubstrate thrombin-binding sites after fibrin clot formation promotes the antithrombotic properties of fibrinogen. Therefore, disorders of fibrinogen may be associated with either a bleeding or a thrombotic predisposition.[4]

Fewer bleeding problems are seen in hypofibrinogenemia and it may not be diagnosed until a traumatic or surgical challenge occurs.[5] In afibrinogenemia, the fibrinogen concentration is <20 mg/dl. In hypofibrinogenemia, the level is less than normal.[6] Intracranial hemorrhage is the main cause of death in these patients. Spontaneous bleeding occurs when the fibrinogen level is <50 mg/dl. All laboratory tests depending on the formation of the clot are prolonged and diagnosis is established by detection of fibrinogen by immunological, chemical, and functional assays. Cryoprecipitate is the mainstay of therapy and a level of 100 mg/dl of fibrinogen is required to obtain normal hemostasis.[6] Fibrinogen deficiency representing about 8% of total rare bleeding disorders worldwide.[7] Pathophysiology: The main determination of pathophysiology is rely on the mutational impact, i.e., the mutation who affecting the synthesis or processing of fibrinogen leads to quantitative fibrinogen disorder, while mutation affecting polymerization, assembly of fibrinolytic system, and cross-linking lead to qualitative disorders.[8] Type I (quantitative) fibrinogen deficiencies are generally inherited as autosomal recessive traits, whereas type II (qualitative) dysfibrinogenemias are inherited as autosomal dominant disorders in most cases.[3]

The aim of the study was to assess the prevalence, demographic parameters, clinical presentation, and hemostatic values in patients diagnosed with congenital fibrinogen deficiency in Haemophilia Centre/Medical city/Baghdad.

Subjects and Methods

This is a retrospective descriptive study of patients who were diagnosed with congenital fibrinogen deficiency in Haemophilia center, Medical City, Baghdad over a period of 7 years from August 2008 to August 2015. Twenty-five patients from all age groups (children and adults) were included in this study. The patients were diagnosed by having normal platelet count, normal bleeding time (PT) prolonged (PT and partial thromboplastin time [PTT]), and confirmation based on low fibrinogen assay. PT and activated PTT (aPTT) are prolonged in afibrinogenemia and may be prolonged in hypofibrinogenemia and dysfibrinogenemia. However, these tests have a poor sensitivity to mild fibrinogen deficiency or dysfunction. In testing for thrombin time, a reagent containing thrombin is added to citrated plasma and the time to clot formation is measured. The thrombin time is prolonged in afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia. This test

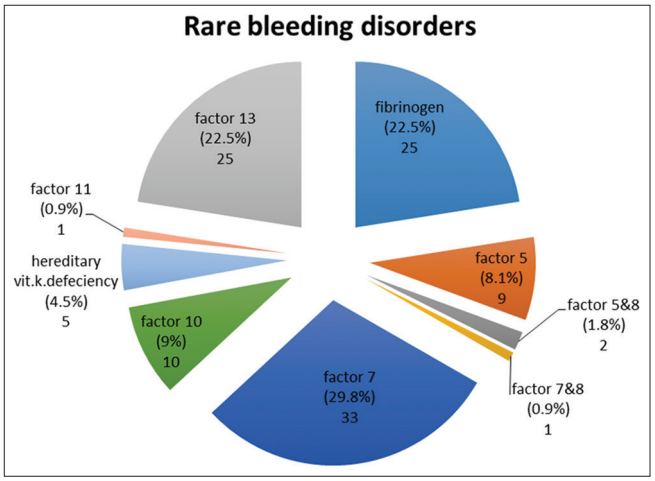

Figure 1: Prevelaence of rare bleeding disorders in hemophilia center in medical city

Table 1: Demographic characteristics of the patients

	n (%)
Age at symptoms onset/years	
≤1	12 (48.0)
1-5	3 (12.0)
>5-10	6 (24.0)
>10	4 (16.0)
Time of diagnosis/months	
≤6	19 (76.0)
>6	6 (24.0)
Afibrinogenemia statues	
A afibrinogenemia (<20 mg/dl)	8 (32.0)
Hypofibrinogenemia (≥20 mg/dl)	17 (68.0)
Family history of fibrinogen deficiency	
Yes	11 (44.0)
No	14 (56.0)
Consanguinity	
Yes	16 (64.0)
No	9 (36.0)
Grade	
1	2 (8.0)
2	8 (32.0)
3	15 (60.0)
Complications	
No complications	20 (80.0)
Hepatitis C infection	3 (12.0)
Hepatitis B infection	1 (4.0)
Died	1 (4.0)

is more sensitive than PT or aPTT for quantitative and qualitative defects in fibrinogen. However, the specificity is poor because a prolonged thrombin time can occur in the presence of heparin, high concentration of fibrin degradation products, and direct thrombin inhibitors. Furthermore, results can significantly vary between laboratories as the test is not standardized.

Clottable fibrinogen

A functional assay by the Clauss method is one of the most common tests used to measure fibrinogen activity. In this method, a reagent containing a high concentration of thrombin that triggers clot formation when added to citrated plasma is used. The time to clot formation is recorded and is read off of a reference curve for tests performed with known concentrations of fibrinogen. Most laboratories these days perform this test on instruments with a photo-optical endpoint analyzer, and lipemia and/or hyperbilirubinemia may interfere with this assay.

Fibrinogen antigen

Various immunoassays are commercially available for the quantitative measurement of fibrinogen assay. These assays do not assess fibrinogen function. In afibrinogenemia, fibrinogen concentrations are low using the clottable or quantitative antigen method, usually <0.1 g/L, and often undetectable in symptomatic individuals. In dysfibrinogenemia, a discrepancy may be found between fibrinogen measured in a functional assay (low) and fibrinogen measured immunologically (normal); however, in some dysfibrinogenemias, a concordant decrease in the 2 assays is observed. A fibrinogen antigen–to–clottable fibrinogen ratio may help to distinguish dysfibrinogenemia (high ratio) from hypofibrinogenemia (ratio close to 1).[9]

Genotyping

Genotyping identification of the specific molecular defect may be useful in both afibrinogenemia and dysfibrinogenemia. Mutation analysis has not identified any correlation with phenotype or ethnic background. However, it can be useful in diagnosis confirmation, screening of relatives for carrier status, family counseling, and prenatal diagnosis.[9] Genotyping is not available in Iraq.

Patient's diagnosis

All the fibrinogen deficient patients were diagnosed on basis of having fibrinogen level <(150 mg/dl).[9] Patients with acquired fibrinogen deficiency secondary to (liver disease, DIC, histiocytosis, and drugs) were excluded from this study. The normal plasma concentration of fibrinogen is approximately 2.0–4.5 g/L g/L (200–450 mg/dl), in our study, patients without detectable fibrinogen protein or cases of fibrinogen level <20 mg/dl were diagnosed as afibrinogenemia and patients with fibrinogen plasma level ≥20 mg/dl and (<150 mg/dl) were diagnosed as hypofibrinogenemia.[9]

All the laboratory tests were performed at coagulation laboratory in the hemophilia ward, children Welfare Teaching Hospital, Medical city, Baghdad. Beside internal quality control, the laboratory test is regularly participating in external quality assessment by the UK National External Quality Assessment Scheme. The fibrinogen level was measured by Clauss assay.

Results

With the exception of thrombasthenia (111), cases of rare bleeding disorders were registered in hemophilia center in medical city-Baghdad, we had (25) cases of congenital fibrinogen deficiency which represents (22.5%) of the registered rare bleeding disorders [Figure 1]. A total of 25 patients with mean age of 15.4 ± 10.1 standard deviation years were included in this study. Eight patients (32%) had fibrinogen level <20 mg/dl (afibrinogenemia) and seventeen patients (68%) had fibrinogen level between (20 and 150 mg/dl) (hypofibrinogenemia) [Table 1]. Males were 17 (68%) of patients and females were 8 (32%) of patients with congenital fibrinogen deficiency.

There were 11 males and 6 females patients with hypofibrinogenemia and 6 males and 2 females with afibrinogenemia, the difference was not significant ($P = 0.6$).

Regarding the onset of presenting symptoms, the highest percentage of the patients presented with symptoms of the disease was within the 1st year of their age 12 patients (48%), 3 patients (12%) presented between 1 and 5 years of age, 6 patients (24%) presented from more than 5 years to 10 years and 4 patients (16%) presented after 10 years old (the oldest age was 49 years).

It was found that 19 patients (76%) were diagnosed within <6 months of the first presentation and 6 patients (24%) were diagnosed after 6 months of presentation. The results also demonstrated that 11 patients (44%) with a positive family history of the disease and 16 patients (64%) had a positive consanguinity (2nd degree consanguinity).

Regarding the grading of fibrinogen deficiency, it was found that just 2 patients (8%) of the patients were in grade one, 8 patients (32%) in grade two, and 15 patients (60%) in grade three.

For the complications, this study showed that 20 patients (80%) were free from any complications, just one (4%) was died due to GIT bleeding (he was 10 years old male known case of hypofibrinogenemia in grade three died at the time of arrival to the emergency unit due to sever hematemesis and shock status) and others were complicated with viral hepatitis.

Regarding presenting symptom, the results showed that the highest percentage of the patient's first presentation was umbilical bleeding in 8 patients (32%) followed by epistaxis in 6 patients (24%), 5 patients (20%) presented with gum bleeding, and 3 patients (12%) presented with hemarthrosis, 3 patients (12%) bleeding after tooth extraction.

Regarding clinical presentation in the recurrent visits to the hemophilia center, we found that the patients with a afibrinogenemia mostly presented with hemarthrosis (22.7%), (18%) presented with muscle hematoma, (14.5%) presented with gum bleeding on recurrent visits, and (13.6%) presented with GIT bleeding and (13.3%) presented with menorrhagia, (11%) with epistaxis and (6.4%) with ecchymosis,(5.4%) of them presented with intra cranial hemorrhage and (3.6%) presented with bleeding at the injection site and (2.7%) presented with bleeding postsurgical.

While patients with hypofibrinogenemia mostly presented with menorrhagia (50.0%), (22%) presented with gum bleeding, and (18%) presented with hemarthrosis, (15%) presented with muscle hematoma and (12%) presented with epistaxis, (9%) presented with ecchymosis, (3.0%) presented either with GIT bleeding or bleeding at the injection site, and (2.0%) presented with bleeding post-surgery.

The results confirmed that the patients who were their symptoms manifested within the 1st year of their age most frequently presented with life-threatening bleeding (4 cases), significant difference was also reported with regards to afibrinogenemia status, while the time to diagnosis did not show an association [Table 2].

The consanguinity showed a significant association with afibrinogenemia (All 8 patients had consanguinity relationship) over hypofibrinogenemia (out of 17, only 8 patients had consanguinity relationship) $P = 0.01$.

The results demonstrated a significant association ($P = 0.001$) between fibrinogenemia status and family history of fibrinogen disorder, all the patients with afibrinogenemia (8 patients) had a positive family history, while 3 patients (17.6%) of those with hypofibrinogenemia had a positive family history.

Regarding the complication, only 2 patients developed complications (hepatitis and death only) and our finding demonstrated that there were found no significant association between the status of fibrinogenemia and complications ($P = 0.1$).

Discussion

In this study, the congenital fibrinogen deficiency representing about (22.5%) of total rare bleeding disorders in hemophilia center, medical city, and this disagrees with Palla *et al*.[10] who reported that the fibrinogen deficiency representing about (8%) of total rare bleeding disorder worldwide but our result was comparable Awidi *et al*.[11] who reported the fibrinogen disorder represented (40%)

Table 2: Relationship between life threating bleeding and some studied parameters

	Life threatening bleeding (*n*=4)		*P*
	Present (row), *n* (%)	Absent (row), *n* (%)	
Age at symptoms onset/years			
≤1	4 (33.3)	8 (66.7)	0.02
>1	0 (0.0)	13 (100.0)	
Time to diagnosis/months			
≤6	4 (21.1)	15 (78.9)	0.2
>6	0 (0.0)	6 (100.0)	
Afibrinogenemia statues			
Afibrinogenemia	3 (37.5)	5 (62.5)	0.04
Hypofibrinogenemia	1 (5.9)	16 (94.1)	

from with total rare bleeding disorders this difference may be because of the prevalence of fibrinogen disorder increase in the population where consanguineous marriages are common.[12] We found that the males were more affected than females (68% males and 32% females) and this is comparable to Peyvandi *et al*.[13] who showed that the male represented (53%) and female (47%). We had 6 females patients in this study above 13 years and all were single.

This study showed that the highest percentage of the patient's first presentation in afibrinogenemia was umbilical bleeding and gum bleeding (37.5%) followed by epistaxis and hemarthrosis which was (12.5%) and this close to De Moerloose *et al*.[14] who showed that the umbilical bleeding represented (60%) from afibrinogenemia first presentation, gum bleeding (30%), epistaxis (12%), and hemarthrosis (30%).

This study confirmed that the patients who were their symptoms manifested within the 1st year of their age most frequently developed life-threatening bleeding (central nervous system bleeding Gastrointestinal tract (GIT) bleeding) we had 4 of 12 cases (33.3%), also life-threatening bleeding was more common in afibrinogenemia 3 of 8 patients (37.5%) while in hypofibrinogenemia only 1 patient of 17 (5.9%) developed GI bleeding and this is close to Peyvandi *et al*.[15] who reported that life-threatening bleeding in afibrinogenemia was (21%) also she reported that GIT bleeding in hypofibrinogenemia was (5%).

This study showed that all patients (100%) with afibrinogenemia had positive consanguinity while 8 out 17 (47.1%) patients with hypofibrinogenemia had positive consanguinity and this agrees with Lak *et al*.[12] who stated that most of his patients come from a consanguineous marriage.

Furthermore, it was found that all patients (100%) with afibrinogenemia had a positive family history of fibrinogen deficiency and this agree with Awidi *et al*.[11] who reported that all 3 patients with afibrinogenemia in his study had positive family history. and also we found just (3 out of 17) (17.6%) patients with hypofibrinogenemia had a positive family history of fibrinogen disorder this disagrees with Awidi *et al*.[11] who reported that (5 out 6) (83.33%) patients with hypofibrinogenemia in his study had a positive family history.

Conclusions

- Congenital fibrinogen deficiency is the second-most common rare bleeding disorders in hemophilia center/medical city
- There is no specific age for presentation of fibrinogen deficiency but there is predominance age group for presentation of ≤1 years
- Most of our patients were diagnosed early within 6 months of the symptoms onset, most of them are normal without complications or chronic disabilities
- The patients whom their symptoms manifested before the 1st year of their age and those with afibrinogenemia most frequently developed life-threating bleeding
- All cases of afibrinogenemia had a positive family history and positive consanguinity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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