Diagnosis, clinical manifestations and management of rare bleeding disorders in Iran

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ABSTRACT

Background: Rare bleeding disorders (RBDs) are heterogeneous disorders, mostly inherited in an autosomal recessive pattern. Iran is a Mideast country with a high rate of consanguinity that has a high rate of RBDs.

Objective: In this study, we present prevalence and clinical presentation as well as management and genetic defects of Iranian patients with RBDs.

Methods: For this study, all relevant publications were searched in Medline until 2015.

Results and discussion: Iran has the highest global incidence of factor XIII deficiency. Factor VII deficiency also is common in Iran, while factor II deficiency, with a prevalence of 1 per ∼3 million, is the rarest form of RBDs. Factor activity is available for all RBDs except for factor XIII deficiency, in which clot solubility remains as a diagnostic test. Molecular analysis of Iranian patients with RBDs revealed a few recurrent, common mutations only in patients with factor XIII deficiency, and considerable novel mutations in other RBDs. Clinical manifestations of these patients are variable and patients with factor XIII, factor X and factor VII more commonly presented severe life-threatening bleeding, while patients with combined factor V and factor VIII presented a milder phenotype. Plasma-derived products are the most common therapeutic choice in Iran, used prophylactically or on-demand for the management of these patients.

Conclusion: Since Iran has a high rate of RBDs with life-threatening bleeding, molecular studies can be used for carrier detection and, therefore, prevention of the further expansion of these disorders and their fatal consequence.

KEYWORDS

Rare bleeding disorder; molecular analysis; clinical manifestations; management

Introduction

Rare bleeding disorders (RBDs) are heterogeneous diseases that are mostly inherited in an autosomal recessive manner and occur owing to the absence or defects of one or more clotting factors, including factor I (FI), factor II (FII), factor V (FV), combined FV and factor VIII (FVIII), factor VII (FVII), factor X (FX), factor XI (FXI), factor XIII (FXIII), and vitamin K-dependent clotting factors. Estimated prevalence of these disorders is 1:500 000 for FVII deficiency (FVIIID) to 1:2 million for FII (FIID) and FXIII deficiency (FXIIIID) worldwide [1–5]. Rare clotting factor deficiencies cause blocking of the coagulation cascade and the subsequently inability to form a clot, resulting in varying bleeding tendency [6,7]. Rare coagulation diseases occur as a result of mutations in the coagulation factor genes with two exceptions, combined FV and FXIII deficiency (CFV-FXIIIID), and combined deficiency of vitamin K-dependent factors (FII, FVII, FIX, and FX). The former exception is caused by mutations in gene-encoding proteins involved in intracellular transport of these factors and the latter occur owing to the mutations of gene-encoding proteins involved in post-translational modifications and vitamin K metabolism [6].

RBDs are categorized into two types. Type 1 deficiencies are more frequently characterized by concomitant reduction in plasma coagulation factor activity and levels. Type 2 deficiencies are qualitative defects. The level of the coagulation factors is normal, slightly reduced or elevated, but their functional activity is reduced [7].

The clinical manifestations that are common to all RBDs are excessive bleeding during or after invasive procedures, such a surgery, circumcision, and dental extraction, and mucocutaneous bleeding, such as epistaxis, gum bleeding, and menorrhagia [8–12]. Routine laboratory coagulation tests used for the investigation and diagnosis of rare coagulation disorders,
except FXIIIID, are prothrombin time (PT) and activated partial thromboplastin time (APTT), thrombin time (TT), and bleeding time (BT), and platelet count are normal [13]. Specific factor activity, used for precise detection of RBDs, and molecular analysis could be used for the confirmation of diagnosis, but in a few cases, an underlying mutation cannot be detected with current sequencing instruments [14,15]. This study focuses on clinical presentations, management and molecular aspects of patients with RBDs in Iran.

**Strategy of search**

For this study, all relevant English language papers were searched in Medline, using appropriate keywords, including recessive bleeding disorders in Iran, rare bleeding disorders in Iran, rare inherited disorders in Iran, factor 1 deficiency in Iran, Factor I deficiency in Iran, FII Deficiency in Iran, Fii deficiency in Iran and F11 deficiency, fibrinogen deficiency in Iran, fibrinogen disorders in Iran, factor 2 deficiency in Iran, Factor II deficiency in Iran, FII Deficiency in Iran, Fii deficiency in Iran and F11 deficiency, factor XIII deficiency in Iran, Factor XIII deficiency in Iran, FXI Deficiency in Iran, Fxi deficiency in Iran and F11 deficiency, Factor XI deficiency in Iran, FXI Deficiency in Iran, Fxi deficiency in Iran and F11 deficiency, factor 7 deficiency in Iran, Factor VII deficiency in Iran, FVII Deficiency in Iran, Fvii deficiency in Iran and F7 deficiency, factor 5 and 8 deficiency in Iran, combined factor 5 and 8 deficiency in Iran, Factor V and VIII deficiency in Iran, FV-VIII Deficiency in Iran, Fv-viii deficiency in Iran and F5 and F8 deficiency, combined coagulation factor deficiency in Iran, factor 10 deficiency in Iran, Factor X deficiency in Iran, FX Deficiency in Iran, Fx deficiency in Iran and F10 deficiency, factor11 deficiency in Iran, Factor XI deficiency in Iran, FXI Deficiency in Iran, Fxi deficiency in Iran and F11 deficiency, factor 11 deficiency in Iran, Factor XI deficiency in Iran, FXI Deficiency in Iran, Fxi deficiency in Iran and F11 deficiency in Iran, hemophilia C, factor 7 and 10 deficiency in Iran, combined factor 7 and 10 deficiency in Iran, Factor VII and X deficiency in Iran, FVII-FX Deficiency in Iran, Fvii-fx deficiency in Iran and F7 and F10 deficiency, factor13 deficiency in Iran, Factor XIII deficiency in Iran, FXIII Deficiency in Iran, Fxiii deficiency in Iran and F13 deficiency, factor 13 deficiency in Iran, and Factor XIII deficiency in Iran, in the title or abstract. To avoid missing data, the same keywords were used in Google Scholar. Frequency of RBDs in Iran is calculated by dividing the WHF 2014 survey’s reported number of RBDs by the total Iranian population.

**Results**

After an extensive search, a total of 42 articles were found. After careful assessment, six of the articles were excluded due to wide overlap with other selected studies and their study populations; and four were excluded due to duplication. Finally, 34 articles were selected for the study.

**Rare bleeding disorders in Iran**

Iran, a Middle Eastern country with a high rate of consanguinity, has a relatively high rate of recessive inheritance disorders. Several studies in Iran have revealed that Iran has a high rate of RBDs [16–18]. Iran has the highest global incidence of FXIIIID and among the highest rates of FVIIID [18,19]. The real distribution pattern of RBDs is not established in Iran and few studies of Iranian patients with RBDs have been performed. Most of those studies were focused on clinical presentations. Molecular analyses of Iranian patients with RBDs were performed on some patients; the exact number is unclear, most of the studies were performed in three areas: southeastern, southern, and northeastern Iran [16,17,20].

**Diagnosis of rare bleeding disorders in Iran**

Diagnosis of RBDs in Iran is based on clinical presentations, family history, and appropriate laboratory tests (Table 1) [2,16].

Molecular analysis of patients with RBDs is not routinely performed in Iranian patients, but molecular analyses are available for patients with FXIIIID, especially in the southeast, which has the highest global incidence of the disorder. A few molecular studies were performed in Iranian patients with FID, FVD, FXD as well as CFV-FVIIID and FXID. No molecular study was performed in FVIIID and FIID [4,21–25].

### Factor I deficiency

A few cases of congenital fibrinogen disorders have been reported, including nine, eight, and two patients from southern, southeastern, and northeastern Iran. All patients from southeastern and northeastern Iran had hypofibrinogenemia and afibrinogenemia, respectively, whereas in southern Iran, of nine patients with fibrinogen disorders, only two were specifically

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**Table 1.** Routine and specific coagulation tests available in Iranian coagulation laboratories [2,4,5].

| General coagulation tests | Specific coagulation assays |
|--------------------------|-----------------------------|
| Prothrombin time (PT)    | Clauss fibrinogen assay     |
| Activated partial thromboplastin time (APTT) | Factor II assay |
| Thrombin time (TT)       | Factor V assay              |
| Reptilase time (RT)      | Factor VII assay            |
| Kaolin clotting time (KCT) | Factor VIII assay |
| Mixed prothrombin time (Mixed PT) | Factor X assay |
| Mixed activated partial thromboplastin time (mixed APTT) | Factor XI assay |
| Clot solubility test     | –                           |
determined to have afibrinogenemia. All patients from southeastern and northeastern Iran, and two patients with afibrinogenemia from southern Iran, were negative for blood-borne diseases. Eight patients from the southeast and two patients with afibrinogenemia from the northeast received cryoprecipitate as prophylaxis. Clinical presentations of two later patients, including a 17-year-old, presented with ecchymosis, menorrhagia, and post-dental extraction bleeding; the second patient was a 30-year-old male with ecchymosis and hemarthrosis [16–18]. Recently, an Iranian 9-day-old baby with umbilical cord bleeding has been reported [5]. Molecular analysis of three Iranian patients with afibrinogenemia led to the identification of a 3282C→T nonsense mutation in exon II of the fibrinogen αβ-chain gene. In two of the three patients, two small deletions, including 4209delA and 4220delT in exon 5 of the fibrinogen αα-chain gene, also were observed [21].

**Prothrombin deficiency**

A few studies were performed in Iranian patients with prothrombin deficiency; no data about the molecular mechanisms of FIIID are available for Iranian patients. Several reports are available about the spectrum of RBDs in different parts of Iran, but no patients with FIIID were reported from southern and northeastern Iran and only one patient with this factor deficiency was reported from northwestern Iran [17,18,26]. Only three patients with FIIID were reported from the southeast. These patients received only on-demand replacement therapy with FFP [16]. Even a World Federation of Hemophilia (WFH) survey in 2013 revealed that it is the rarest inherited bleeding disorder in Iran and only 24 patients with this disorder were reported at the time [1].

According to the 2013 WFH survey, FIIID comprises (1.7%) of RBDs in Iran. That is inconsistent with our literature review.

**Factor V deficiency**

According to the WFH survey, there are 147 patients with FVD in Iran. A search in the literature found 96 patients in different parts of Iran, but some overlap in reported cases may be present. Out of 96 patients, underlying gene defects were determined in four patients. These mutations included IVS8 + 6T > C, IVS21 + 1G > A, IVS24 + 1_ + 4delGTAG, and IVS19 + 3A > T [24,25]. A wide spectrum of clinical presentations were observed in Iranian patients with FVD. A considerable number of Iranian patients with severe FVD have mild bleeding, such as epistaxis, while others with same FV level have life-threatening episodes of CNS and umbilical cord bleeding [17,25,27–31] (Table 2).

Some rare clinical presentations also were observed in Iranian patients. These include CNSB and recurrent miscarriage. Three patients with FVD had mental retardation. Two of them had mild FV deficiency, while the other had moderate deficiency. FFP is used in the management of patients with FVD in Iran [17,28,31].

Most reported cases from southeast Iran had mild to moderate FVD, while most of the reported cases from central and northeastern Iran have moderate to severe deficiency [17,28,30].

**Combined factor V–VIII deficiency**

Ninety-five Iranian patients with CFV-FVIID were found in the literature, but the origin of some patients was not mentioned. Because of this, an overlap may be present in reported cases (28 cases) [16]. Out of 95 cases, 28, 12, 4, and 2 cases were reported from northeast, south, southeast and northwest Iran; origin of the rest was not specified. Among Iranian patients, epistaxis and post-dental extraction bleeding are the most common presentations. Most reported cases had both FV and FVIII activity levels between 5 and 20%. Molecular analysis of 12 patients with CFV-FVIID revealed that, in these patients, splice-site mutation is the most common form of gene defect. Frameshift and nonsense mutations are other gene defects among Iranian patients [16–18,22,32–36] (Table 2).

**Factor VII deficiency**

According to the 2013 WFH survey, FVIIID, with 470 cases, is the most common RBD among Iranian patients. But in a national survey FXIIIID, with 483 cases, is cited as the most common RBD in Iran [4]. In the literature, 93 cases with FVIIID were found in different parts of Iran, including the southeastern, northwestern, northern, and northeastern regions, with some overlaps [16–18,26,37]. Iranian patients with FVIIID presented a variety of bleeding episodes including epistaxis, as the most common symptom, as well as hemarthrosis, post-dental extraction bleeding, gastrointestinal (GI) bleeding, and hematuria. No published data about the molecular basis of FVIIID in Iranian patients were available. Most Iranian patients with FVIIID had plasma FVII activity below 5%. Different therapeutic choices, including FFP, prothrombin complex concentrate (PCC), and recombinant FVII (rFVII), are available for Iranian patients with FVIIID. Recently, an Iranian rFVII (Aryoseven) was produced and successfully used in Iranian patients [16–18,26,37,38,40].

**Factor X deficiency**

In the literature, 90 Iranian patients with FXD were reported, with some overlap, because in all studies
the patients’ origin was not mentioned. Most of the studies were focused on clinical presentations and management of the bleeds. A few studies reported on the molecular basis of FXD. Iranian patients with FXD presented severe bleeding episodes [17,23,39,40,41]. In two cases reported from northeastern Iran, the first experienced umbilical cord bleeding and two CNSBs, the other experienced GI bleeding with hemarthrosis and hematoma as well as ecchymosis and post-dental extraction bleeding [17]. In the southeast of Iran, out of five reported cases with FXD, three cases experienced intraventricular and intracranial hemorrhages (ICH) in spite of prophylaxis with 15–20 mL kg⁻¹ FFP [16]. In a study of 10 Iranian patients with severe FXD (FX activity < 1%), a dose of 20 IU kg⁻¹ of FX concentrate (CSL Behring, Marburg, Germany) was used successfully for prophylaxis. It concluded that the dose of 20 IU kg⁻¹ of FX

| Disorder | Number of patients (WFH) | Number of patients (literaturea) | Clinical presentations | Gene defects | Type of replacement therapyb | Dose of treatmentb |
|----------|--------------------------|----------------------------------|-----------------------|-------------|-----------------------------|-------------------|
| FI deficiency | 107 | 25 | Umbilical cord bleeding Epistaxis GI bleeding Hematuria Intracranial hemorrhage | 3282C→T 4209delA 4220delT | Prophylaxis | 100 mg kg⁻¹ per every 2 weeks with CP |
| FI deficiency | 24 | 4 | Epistaxis Hematoma GI bleeding Post-partum bleeding Menorrhagia CNS bleeding Umbilical cord bleeding Recurrent miscarriage Hematuria Hemarthrosis ICH | 85B8 + 6T > C IVS21 + 1G > A IVS24 + 1, + 4delGAG IVS519 + 3A > T | On-demand | 15–20 mL kg⁻¹ FFP FFP (15–20 mL kg⁻¹) |
| FV deficiency | 147 | 96 | Epistaxis Hematoma GI bleeding | c.822G > A c.904A > T (p.Lys302X) | On-demand | FFP (15–30 mL kg⁻¹) |
| FVI deficiency | 470 | 93 | Epistaxis Post-dental extraction bleeding Hemarthrosis CNS bleeding | – | – | NM |
| FX deficiency | 153 | 90 | Epistaxis CNS bleeding Hemarthrosis GI bleeding Hematoma | Cys81Tyr Gly94Arg Asp95Glu Gly222Asp Glu69Lys Asp103His | Prophylaxis (Severe deficiency) | FFP (15–20 mL kg⁻¹) |
| FXI deficiency | 152 | 53 | Hemarthrosis Hematoma Epistaxis | 1169C > G (Gly342Ala) 1693G > A (Glu547Lys) 403G > T (Glu134Stop) | On-demand | FFP (10 mL kg⁻¹) |
| FXII deficiency | 205 | 483 | Umbilical cord bleeding Intracranial hemorrhage Miscarriage Hemarthrosis Hematoma | c.562T > C (Trp187Arg) c.120G > A (Arg77His) c.868C > T (Arg293Cys) c.699G > A (Arg233His) c.1236G > T (Arg382Ser) | Prophylaxis | FFP: 10 mL kg⁻¹ every 28–30 days CP: One bag per 10–20 kg Fibrogammin: 10–26 IU/kg |
| FVII–FX deficiency | 0 | 3 | Umbilical cord bleeding GI bleeding Hematoma | FX: Ser3Cys FVII: Cys310Phe | – | |
| FVII–FXIII deficiency | 0 | 1 | Umbilical cord bleeding | FXIII: Trp187Arg FVII: Unknown | Prophylaxis | |

aReported cases may have some overlap because all studies did not mention precise origin of patients.
bThese data are based on reference number 16.
concentrate is the best therapeutic choice for patients with severe FXD who need regular prophylaxis [42]. A few molecular studies were performed on Iranian patients with FXD; full molecular characteristics of these patients has been previously reported. Briefly, the most common FX gene mutations in Iranian patients are missense mutations and splice-site mutations. Most of the FX gene mutations are new and unique to a patient or a family [43] (Table 3).

**Factor XI deficiency**

Although 152 Iranian cases with FXID were reported by the WFH in 2013, literature review shows a significantly lower number: and only one and two cases with FXID were reported from southeastern and northeastern Iran [16,17]. Seven cases with FXID were reported in northern Iran and in a study of 502 bleeding disorders in southern Iran, five cases with FXID were detected. Among them, a causative mutation was detected only in two patients without inhibitor development [20]. In a study on 38 Iranians, without definitive origin of the patients, oral cavity bleeding, postoperative bleeding and epistaxis as well as hemorrhosis and hematoma were reported as clinical presentations [44] (Table 3).

A clear relationship between FXI activity and plasma level with severity of clinical presentation in Iranian patients was not observed and this issue was reported [44].

**Factor XIII deficiency**

FXIIID, with 483 reported cases, is the most common RBD in Iran [4]. According to WFH’s 2013 survey, 1239 patients with FXIIID are known worldwide and Iran, with 483 patients, has about one-third of the world’s patients. We previously reported on the situation of FXIIID in Iran in detail [4]. Among Iranian patients, umbilical cord bleeding is the most common clinical presentation. ICH and hematoma are other common presentations. Management of patients with FXIIID in Iran makes use of FFP, cryoprecipitate and Fibrogammin® P. Fibrogammin® P with a dose of 10–26 IU/Kg is used for the management of ICH in FXIIID and with a dose of 10 IU/Kg for the management of miscarriage. Molecular analysis of Iranian patients with FXIIID led to the identification of several mutations, including Trp187Arg and Arg77His the most common mutations among Iranian patients [4,12] (Table 2).

**Combined factor X and factor VII**

Three Iranian patients with CFVII-FXD were reported; in two cases underlying mutations were detected in genes of both factors and the third one was not molecularly assessed. Unlike in CFV-VIIID, all three patients with CFVII-FXD had severe bleeding episodes, such as umbilical cord bleeding, GI bleeding, and hematoma as well as menstruation [45,46]. A very rare case with combined FVII-FXIII deficiency was reported from the southeast of Iran [45].

**Discussion**

In Iran, with its high rate of RBDs, only a few specialized centers have the resources and the expertise to diagnose RBDs. Furthermore, for many of these disorders, there are no treatments available to their residents. A significant example for this problem is Khosh city, southeast Iran, which has the highest number of patients with FXIIID. Owing to the lack of appropriate medical services in this city, they have to travel to Zahedan, the provincial center for medical facilities. This is difficult especially for those people in rural areas of Khosh whose economic situation is poor [7,47,48].

Iran’s high rate of consanguineous marriage results in a higher rate of these autosomal recessive bleeding disorders [7]. Iran has the highest global incidence of FXIIID and FVIID is more common in Iran than anywhere else (Table 3) [49].

Diagnosis of most patients with RBDs is performed by standard methods in Iran, but these resources are provided by reference centers and are not available in all areas. Factor activity assay is available for all RBDs except FXIIID, which is diagnosed by the clot solubility test in Iran. Factor antigen assay is not routinely performed in Iran even for FIID and FI disorders and physicians have to rely on clinical presentations for proper diagnosis, but this is not a standard procedure [50]. Molecular diagnosis is not routinely performed

### Table 3. The comparisons between incidence of RBDs in Europe, Worldwide, and Iran. ([https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Other-Factor-Deficiencies](https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Other-Factor-Deficiencies)).

| Missing factor       | Incidence in Iran | Incidence worldwide | Incidence in Europe |
|----------------------|-------------------|---------------------|---------------------|
| Factor I             | 1.7 in 1 000      | 1 or 2 in 1        | 5 in 10            |
| Afibrinogenemia      | 000               | 000.000            | 000.000            |
| Hypofibrinogenemia   | Not available     | 1 in 1 000         | 000               |
| Dysfibrinogenemia    |                   | 000                |                    |
| Factor II            | 0.3 in 1 000      | 1 in 2 000         | 1 in 2 000         |
| Factor V             | 2.3 in 1 000      | 1 in 1 000         | 1 in 1 000         |
| Combined factor V and factor VIII | 2.8 in 1 000 | 1 in 1 000 | 1 in 1 000 |
| Factor VII           | 7.4 in 1 000      | 1 in 500.000       | 1 in 500.000       |
| Factor X             | 2.1 in 1 000      | 1 in 500.000       | 1 in 1 000         |
| Factor XI            | 2.4 in 1 000      | 1 in 100.000       | 1 in 100.000       |
| Factor XIII          | 2.9 (5.5) in 1 000 000 | 1 in 2 000 | 1 in 3 000 |

*According to reported number in the literature.
for confirmation of RBDs except for established molecular methods for diagnosis of FXIII, carrier detection and prenatal diagnosis in southeast Iran. Owing to the founder effect, all patients with FXIIIID in this area have a unique mutation of c.562t > c in exon 4 of the FXIII-A gene [7,51,52]. A considerable number of standard therapeutic choices are available in Iran and are routinely used. Fibrogammin and PCC are available for the treatment of patients with FXIIIID and FXD and FIIID, respectively [49]. rFVII as bypassing agent, accompanied with other local agents, such as antifibrinolytic drugs, is also available. Most patients with RBDs get on-demand therapy in Iran except, FXIIIID patients, who get Fibrogammin as prophylaxis [49]. Patients with hemophilia routinely get on-demand therapy and a considerable number of them have been affected with blood-borne disease, while this number is much lower in RBDs [2,49].

Conclusion
Owing to the high rate of consangunuity, Iran has high rate of RBDs, but the precise prevalence of these disorders and the molecular basis of most cases is not clear. Since a considerable number of these patients present life-threatening bleeding, molecular studies can be used for carrier detection and, therefore, prevention of the further expansion of these disorders and their fatal consequence.

Disclosure
No potential conflict of interest was reported by the authors.

Ethics approval
This study was approved by the medical ethics committee of Iran University of Medical Sciences.

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