

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 Medlin 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 (FXIIID) 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 FVIII deficiency (CFV-FVIIID), 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 FXIID, 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, FI Deficiency in Iran, Fi deficiency in Iran and F1 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 F2 deficiency, thrombin deficiency in Iran, prothrombin deficiency in Iran, factor 5 deficiency in Iran, Factor V deficiency in Iran, FV Deficiency in Iran, Fv deficiency in Iran and F5 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-FVIII Deficiency in Iran, Fv-fviii 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 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,

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 (APT)	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	-

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 46 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 six 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 FXIID and among the highest rates of FVIID [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 presentation. 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 presentation, 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 FXIID, 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-FVIID and FXID. No molecular study was performed in FVIID 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 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 $\beta\beta$ -chain gene. In two of the three patients, two small deletions, including 4209delA and 4220delT in exon 5 of the fibrinogen $\alpha\alpha$ -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 FIID are available for Iranian patients. Several reports are available about the spectrum of RBDs in different parts of Iran, but no patients with FIID 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 FIID 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, FIID 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-FVIII 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-FVIII 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 FXIIID, 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, 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].

Table 2. Characteristics of Iranian patients with RBDs.

Disorder	Number of patients (WFH)	Number of patients (literature ^a)	Clinical presentations	Gene defects	Type of replacement therapy ^b	Dose of treatment ^b	
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	390
FII deficiency	24	4			On-demand	15–20 mL kg ⁻¹ FFP	
FV deficiency	147	96	Epistaxis Hematoma GI bleeding Post-partum bleeding Menorrhagia CNS bleeding Umbilical cord bleeding Recurrent miscarriage Hematuria Hemarthrosis	IVS8 + 6T > C IVS21 + 1G > A IVS24 + 1_ + 4delGTAG IVS19 + 3A > T	On-demand	FFP (15–20 mL kg ⁻¹)	395
FV-VIII deficiency	190	95	Epistaxis Hemarthrosis CNS bleeding GI bleeding	c.822G > A c.904A > T (p.Lys302X) c.1261_1262insTG c.89–90insG	On-demand	FFP (15–30 mL kg ⁻¹)	405
FVII 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)	410
FXI deficiency	152	53	Hemarthrosis Hematoma Epistaxis	1169G > C (Gly372Ala) 1693G > A (Glu547Lys) 403G > T (Glu117Stop)	On-demand	FFP (10 mL kg ⁻¹)	415
FXIII deficiency	205	483	Umbilical cord bleeding Intracranial hemorrhage Miscarriage Hemarthrosis Hematoma	c.559T > C (Trp187Arg) c.320G > A (Arg77His) c.868C > T (Arg260Cys) c.869G > A (Arg260His) 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	420
FVII-FX deficiency	0	3	Umbilical cord bleeding GI bleeding Hematoma	FX: Ser3Cys FVII: Cys310Phe			425
FVII-FXIII deficiency	0	1	Umbilical cord bleeding	FXIII: Trp187Arg FVII: Unknown	Prophylaxis		430

^aReported cases may have some overlap because all studies did not mention precise origin of patients.

^bThese data are based on reference number 16.

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 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 hemarthrosis 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].

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>).

Missing factor	Incidence in Iran	Incidence worldwide	Incidence in Europe
Factor I	1.7 in 1 000 000	1 or 2 in 1 000 000	5 in 10 000 000
Afibrinogenemia			Not available
Hypofibrinogenemia			1 in 1 000 000
Dysfibrinogenemia			000
Factor II	0.3 in 1 000 000	1 in 2 000 000	1 in 2 000 000
Factor V	2.3 in 1 000 000	1 in 1 000 000	1 in 1 000 000
Combined factor V and factor VIII	2.8 in 1 000 000	1 in 1 000 000	1 in 1 000 000
Factor VII	7.4 in 1 000 000	1 in 500 000	1 in 500 000
Factor X	2.1 in 1 000 000	1 in 500 000 to 1 000 000	1 in 1 000 000
Factor XI	2.4 in 1 000 000	1 in 100 000	1 in 100 000
Factor XIII	2.9 (6.5 ^a) in 1 000 000	1 in 2 000 000	1 in 3 000 000

^aAccording to reported number in the literature.

Factor XIII deficiency

FXIIID, with 473 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 473 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 menorrhagia [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 Khash 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 Khash whose economic situation is poor [7, 47, 48]. Palla *et al* are investigating the general features of RBDs [6].

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 FVIIID 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 for confirmation of RBDs except for established molecular methods for diagnosis of FXIIID, carrier detection and prenatal diagnosis in southeast Iran. **Qwing** to the founder effect, all patients with FXIIID in this area have a unique mutation of c.559t > 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 FXIIID and FXD and FIID, 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, FXIIID 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

Qwing to the high rate of consanguinity, 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

AQ2 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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