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Diagnosis, Clinical Manifestations and Management of Rare Bleeding Disorders in Iran

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Diagnosis, Clinical Manifestations and Management of Rare Bleeding Disorders in Iran

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 management of these patients.

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Conclusion: Since Iran has 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 due 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 (VKCFD). Estimated prevalence of these disorders is 1:500,000 for FVII deficiency (FVIID) 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-FVIIIID), 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 due to the mutations of gene-encoding proteins involved in post-translational modifications and vitamin K metabolism (6).

RBDs are categorized in two types. Type 1 deficiencies are more frequently characterized by concomitant reduction in plasma coagulation factor activity and levels. Type 2 deficiencies are

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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 as surgery, circumcision and dental extraction, and mucocutaneous bleeding such as epistaxis, gum bleeding and menorrhagia (8-12). Routine laboratory coagulation tests used for investigation and diagnosis of rare coagulation disorders, except FXIID, are prothrombin time (PT) and activated partial thromboplastin time (APTT), thrombin time (TT), 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 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

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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, 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, 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 country has a high rate of RBDs (16-18). Iran has the highest global incidence of FXIIID and among the highest rates of

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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 north-eastern 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).

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	-

Molecular analysis of patients with RBDs is not routinely performed in Iranian patients but molecular analyses are available for patients with FXIIID, 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).

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Factor I deficiency

A few cases of congenital fibrinogen disorders have been reported, including nine, eight and two patients from southern, southeastern and north-eastern 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 nine-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 B β -chain gene. In two of the three patients, two small deletions, including 4209delA and 4220delT in exon 5 of the fibrinogen A α -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 [Type text]

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 was 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).

Table 2. Characteristics of Iranian patients with rare bleeding disorders

Disorder	Number of patients (WFH)	Number of patients (literature*)	Clinical presentations	Gene defects	Type of replacement therapy**	Dose of treatment **
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
FII deficiency	24	4			On-demand	15–20 mL kg-1 FFP

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FV deficiency	147	96	Epistaxis Hematoma GI bleeding Postpartum 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)
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)
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)
FXI deficiency	152	53	Hemarthrosis Hematoma Epistaxis	1169G>C (Gly372Ala) 1693G>A (Glu547Lys) 403G>T (Glu117Stop)	On-demand	FFP (10 mL kg ⁻¹)
FXIII deficiency	205	483	Umbilical cord bleeding Intracranial hemorrhage Miscarriage Hemarthrosis Hematoma	c559T > C (Trp187Arg) c320G > A (Arg77His) c868C > T (Arg260Cys) c869G > A (Arg260His) c1236G > 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	

*Reported cases may have some overlap because all studies did not mention precise origin of patients

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**These data are based on reference number 16

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-FVIIIID 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% to 20%. Molecular analysis of twelve patients with CFV-FVIIIID 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

*Reported cases may have some overlap because all studies did not mention precise origin of patients

**These data are based on reference number 16

(16-18, 26, 37). Iranian patients with FVIIID presented a variety of bleeding episodes including

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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 FVIID in Iranian patients were available. Most Iranian patients with FVIID 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 FVIID. 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, ninety 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 ten 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

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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 2 patients without inhibitor development (20). In a study on 38 Iranians, without definitive origin of the patients, oral cavity bleeding, post-operative 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).

Factor XIII deficiency

FXIID, with 473 reported cases, is the most common RBD in Iran (4). According to WFH's 2013 survey, 1,239 patients with FXIID are known worldwide and Iran, with 473 patients, has about one-third of the world's patients. We previously reported on the situation of FXIID 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 FXIID in Iran makes use of FFP, cryoprecipitate and Fibrogammin® P. Fibrogammin® P with a dose of 10–26 IU/Kg is used for management of ICH in FXIID and with a dose of 10 IU/Kg for management of miscarriage. Molecular analysis of Iranian patients with FXIID led to the

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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 both factors' genes 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. Due to a 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 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).

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>)

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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	
Afibrinogenemia			5 in 10,000,000
Hypofibrinogenemia			Not available
Dysfibrinogenemia			1 in 1,000,000
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*) in 1,000,000	1 in 2,000,000	1 in 3,000,000

*According to reported number in the literature

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 FXIID, 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

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procedure (50). Molecular diagnosis is not routinely performed for confirmation of RBDs except for established molecular methods for diagnosis of FXIID, carrier detection and prenatal diagnosis in southeast Iran. Due to the founder effect all patients with FXIID 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 Prothrombin complex concentrate (PCC) are available for treatment of patients with FXIID and FXD and FIID respectively (49). rFVII as bypassing agent, accompanied with other local agents such as antifibrinolytic drugs, also are available. Most patients with RBDs get on-demand therapy in Iran except, FXIID 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

Due 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.

Abbreviations

APTT, activated partial thromboplastin time; BT, bleeding time; CNS, central nervous system

FFP, Fresh frozen plasma; ICH, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ISTH, International Society of Thrombosis and Haemostasis; PT, prothrombin time; RBDs, Rare Bleeding Disorders; RT, reptilase time; TT, thrombin time; WFH, World Federation of Hemophilia.

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Ethics Approval and Consent to Participate

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

Consent for publication

Not applicable

Availability of data and materials

The data set supporting the results of this article are included within the article and Additional files 1 and 2. File 1 is Figure 1. Prevalence of rare bleeding disorders (RBDs) in Iran is based on the 2013 annual report of the World Federation of Hemophilia (WFH) survey (1). File 2 is include of Table 1 - Routine and specific available coagulation tests in Iranian coagulation laboratories (2, 4, 5) , Table 2 - Classification of Rare Bleeding Disorders (RBDs) according to ISTH recommendation (3), Table 3 - Characteristics of Iranian patients with rare bleeding disorders and Table 4-The cincidence of RBDs in Europe, Worldwide and Iran (<https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Other-Factor-Deficiencies>).

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

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AD managed the whole research process, participated in every phase of the systematic review and drafted the initial manuscript. ST participated in the conceptualization and planning of the study, supervised the review process and contributed in writing the manuscript. MSH participated in the phase of discussion and critically reviewed the manuscript. ShS and MS took part in the systematic review process, participated in the discussion, and contributed in writing and reviewing the manuscript. Daisy Morant edited the English version of this manuscript.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

1. Skinner M, Myles E. World Federation of Hemophilia: 50 years of advancing treatment for all. *Haemophilia*. 2014;19(4):475-80.
2. Dorgalaleh A, Dadashizadeh G, Bamedi T. Hemophilia in Iran. *Hematology*. 2016:1-11.
3. Peyvandi F, Di Michele D, Bolton-Maggs P, Lee C, Tripodi A, Srivastava A. Classification of rare bleeding disorders (RBDs) based on the association between coagulant factor activity and clinical bleeding severity. *Journal of Thrombosis and Haemostasis*. 2012;10(9):1938-43.
4. Dorgalaleh A, Naderi M, Hosseini MS, Alizadeh S, Hosseini S, Tabibian S, et al., editors. Factor XIII Deficiency in Iran: A Comprehensive Review of the Literature. *Seminars in thrombosis and hemostasis*; 2015.
5. Abolghasemi H, Shahverdi E. Umbilical bleeding: a presenting feature for congenital afibrinogenemia. *Blood coagulation & fibrinolysis*. 2015;26(7):834-5.
6. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. *Blood*. 2015:blood-2014-08-532820.

[Type text]

7. Naderi M, Tabibian S, Hosseini MS, Alizadeh S, Hosseini S, Karami H, et al. Rare bleeding disorders: a narrative review of epidemiology, molecular and clinical presentations, diagnosis and treatment. *Journal of Pediatrics Review*. 2014;2(2):0-.
8. Acharya S, Coughlin A, Dimichele D. Rare Bleeding Disorder Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. *Journal of Thrombosis and Haemostasis*. 2004;2(2):248-56.
9. Acharya S, Dimichele D. Rare inherited disorders of fibrinogen. *Haemophilia*. 2008;14(6):1151-8.
10. Lancellotti S, De Cristofaro R, editors. Congenital prothrombin deficiency. *Seminars in thrombosis and hemostasis*; 2009.
11. Herrmann F, Wulff K, Auerswald G, Schulman S, Astermark J, Batorova A, et al. Factor VII deficiency: clinical manifestation of 717 subjects from Europe and Latin America with mutations in the factor 7 gene. *Haemophilia*. 2009;15(1):267-80.
12. Naderi M, Dorgalaleh A, Alizadeh S, Tabibian S, Hosseini S, Shamsizadeh M, et al. Clinical manifestations and management of life-threatening bleeding in the largest group of patients with severe factor XIII deficiency. *International journal of hematology*. 2014;100(5):443-9.
13. Kitchen S, McCraw A, Echenagucia M. Diagnosis of hemophilia and other bleeding disorders. *A laboratory manual World Federation of Hemophilia*. 2000:53-6.
14. Hayward CP, Moffat K. Laboratory testing for bleeding disorders: strategic uses of high and low-yield tests. *International journal of laboratory hematology*. 2013;35(3):322-33.
15. Peyvandi F, Jayandharan G, Chandy M, Srivastava A, Nakaya S, Johnson M, et al. Genetic diagnosis of haemophilia and other inherited bleeding disorders. *Haemophilia*. 2006;12(s3):82-9.
16. Naderi M, Eshghi P, Saneei Moghaddam E, Alizadeh S, Dorgalaleh A, Younesi M, et al. Safety of human blood products in rare bleeding disorders in southeast of Iran. *Haemophilia*. 2013;19(2):e90-e2.
17. Mansouritorghabeh H, Manavifar L, Banihashem A, Modaresi A, Shirdel A, Shahroudian M, et al. An investigation of the spectrum of common and rare inherited coagulation disorders in North-Eastern Iran. *Blood Transfusion*. 2013;11(2):233.

[Type text]

18. Karimi M, Haghpanah S, Amirhakimi A, Afrasiabi A, Dehbozorgian J, Nasirabady S. Spectrum of inherited bleeding disorders in southern Iran, before and after the establishment of comprehensive coagulation laboratory. *Blood coagulation & fibrinolysis*. 2009;20(8):642-5.
19. Dorgalaleh A, Tabibian S, Hosseini S, Shamsizadeh M. Guidelines for laboratory diagnosis of factor XIII deficiency. *Blood coagulation & fibrinolysis*. 2016;27(4):361-4.
20. Karimi M, Jafari H, Lahsaeizadeh S, Afrasiabi A, Akbari A, Dehbozorgian J, et al. Factor XI deficiency in Southern Iran: identification of a novel missense mutation. *Annals of hematology*. 2009;88(4):359-63.
21. Asselta R, Spina S, Duga S, Peyvandi F, Malcovati M, Mannucci PM, et al. Analysis of Iranian patients allowed the identification of the first truncating mutation in the fibrinogen Bbeta-chain gene causing afibrinogenemia. *Haematologica*. 2002;87(8):855-9.
22. Karimi M, Cairo A, Safarpour MM, Haghpanah S, Ekramzadeh M, Afrasiabi A, et al. Genotype and phenotype report on patients with combined deficiency of factor V and factor VIII in Iran. *Blood coagulation & fibrinolysis*. 2014;25(4):360-3.
23. Karimi M, Menegatti M, Afrasiabi A, Sarikhani S, Peyvandi F. Phenotype and genotype report on homozygous and heterozygous patients with congenital factor X deficiency. *Haematologica*. 2008;93(6):934-8.
24. Dall'Osso C, Guella I, Duga S, Locatelli N, Paraboschi EM, Spreafico M, et al. Molecular characterization of three novel splicing mutations causing factor V deficiency and analysis of the F5 gene splicing pattern. *Haematologica*. 2008;93(10):1505-13.
25. Asselta R, Montefusco M, Duga S, Malcovati M, Peyvandi F, Mannucci P, et al. Severe factor V deficiency: exon skipping in the factor V gene causing a partial deletion of the C1 domain.

Journal of Thrombosis and Haemostasis. 2003;1(6):1237-44.

update. *Seminars in thrombosis and hemostasis*; 2013.

[Type text]

26. Ziaei J, Dolatkhah R, Dastgiri S, Mohammadpourasl A, Asvadi I, Mahmoudpour A, et al. Inherited coagulation disorders in the northwestern region of Iran. *Haemophilia*. 2005;11(4):424-6.
27. Huang J, Koerper M. Factor V deficiency: a concise review. *Haemophilia*. 2008;14(6):1164-9.
28. Naderi M, Tabibian S, Alizadeh S, Hosseini S, Zaker F, Bamedi T, et al. Congenital Factor V Deficiency: Comparison of the Severity of Clinical Presentations among Patients with Rare Bleeding Disorders. *Acta haematologica*. 2015;133(2):148-54.
29. Naderi M, Tabibian S, Shamsizadeh M, Dorgalaleh A. Miscarriage and recurrent miscarriage in patients with congenital factor V deficiency: a report of six cases in Iran. *International journal of hematology*. 2016:1-3.
30. Mansouritorghabeh H, Manavifar L, Mobalegh A, Shirdel A. Haemorrhagic manifestations and prevalence of factor V deficiency in north-eastern Iran. *Haemophilia*. 2010;16(2):376-80.
31. Lak M, Sharifian R, Peyvandi F, Mannucci P. Symptoms of inherited factor V deficiency in 35 Iranian patients. *British journal of haematology*. 1998;103(4):1067-9.
32. Mansouritorghabeh H. Combined factor V and VIII deficiency. *Iranian journal of medical sciences*. 2015;32(3):131-6.
33. Peyvandi F, Tuddenham E, Akhtari A, Lak M, Mannucci P. Bleeding symptoms in 27 Iranian patients with the combined deficiency of factor V and factor VIII. *British journal of haematology*. 1998;100(4):773-6.
34. MANSOURI TORGHABEH H, POURFATHOLLAH AA, MAHMOODIAN SHOOSHTARI M, REZAIE YAZDI Z, ESMAILI H. FACTOR V AND VIII INHIBITOR IN PATIENTS WITH COMBINED FACTOR V AND VIII DEFICIENCY. *Medical journal of the Islamic Republic of Iran*. 2005;18(4):309-13.
39. Mansouritorgabeh H, Rezaieyazdi Z, Pourfathollah A, Rezai J, Esamaili H. Haemorrhagic symptoms in patients with combined factors V and VIII deficiency in north-eastern Iran. *Haemophilia*. 2004;10(3):271-5.
40. Mansouritorghabeh H, Rezaieyazdi Z, Pourfathollah A. Combined factor V and VIII deficiency: a new family and their haemorrhagic manifestations. *Haemophilia*. 2006;12(2):169-71.

37. Peyvandi F, Mannucci P, Asti D, Abdoullahi M, Di Rocco N, Sharifian R. Clinical manifestations in 28 Italian and Iranian patients with severe factor VII deficiency. *Haemophilia*. 1997;3(4):242-6.
38. Faranoush M, Abolghasemi H, Toogeh G, Karimi M, Eshghi P, Managhchi M, et al. A Comparison Between Recombinant Activated Factor VII (Aryoseven) and Novoseven in Patients With Congenital Factor VII Deficiency. *Clinical and Applied Thrombosis/Hemostasis*. 2014;1076029614522545.
39. Sumer T, Ahmad M, Sumer N, Al-Mouzan M. Severe congenital factor X deficiency with intracranial haemorrhage. *European journal of pediatrics*. 1986;145(1-2):119-20.
40. Peyvandi F, Mannucci P, Lak M, Abdoullahi M, Zeinali S, Sharifian R, et al. Congenital factor X deficiency: spectrum of bleeding symptoms in 32 Iranian patients. *British journal of haematology*. 1998;102(2):626-8.
41. Dorgalaleh A, Zaker F, Tabibian S, Alizadeh S, Dorgalele S, Hosseini S, et al. Spectrum of factor X gene mutations in Iranian patients with congenital factor X deficiency. *Blood coagulation & fibrinolysis*. 2016;27(3):324-7.
42. Karimi M, Vafafar A, Haghpanah S, Payandeh M, Eshghi P, Hoofar H, et al. Efficacy of prophylaxis and genotype-phenotype correlation in patients with severe Factor X deficiency in Iran. *Haemophilia*. 2012;18(2):211-5.
43. Girolami A, Molaro G, Calligaris A, De Luca G. Severe congenital factor X deficiency in 5-month-old child. *Thrombosis et diathesis haemorrhagica*. 1970;24(1):175.
44. Peyvandi F, Lak M, Mannucci PM. Factor XI deficiency in Iranians: its clinical manifestations in comparison with those of classic hemophilia. *Haematologica*. 2002;87(5):512-4.
45. Naderi M, Tabibian S, Hosseini MS, Alizadeh S, Hosseini S, Shamsizadeh M, et al. Congenital combined deficiency of coagulation factors: a study of seven patients. *Blood coagulation & fibrinolysis*. 2015;26(1):59-62.

[Type text]

46. Menegatti M, Karimi M, Garagiola I, Mannucci P, Peyvandi F. A rare inherited coagulation disorder: combined homozygous factor VII and factor X deficiency. American journal of hematology. 2004;77(1):90-1.

47. World Federation of Hemophilia Report on the(ANNUAL GLOBAL SURVEY 2014)

48. M. NADERI, P . ESHGHI, E. SANEEI MOGHADDAM, SH. ALIZADEH, A. DORGALALEH, M. R. YOUNESI, Z. K. KHATEB. Safety of human blood products in rare bleeding disorders in southeast of Iran. The official journal of the world federation of hemophilia. Haemophilia (2013), 19,:

49. Dorgalaleh A, Naderi M, Shamsizadeh M. Morbidity and mortality in a large number of Iranian patients with severe congenital factor XIII deficiency. Annals of hematology. 2016;95(3):451-5.

50. <https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Other-Factor-Deficiencies>

51- Dorgalaleh A, Rashidpanah J. Blood coagulation factor XIII and factor XIII deficiency. Blood reviews. 2016.

52-Dorgalaleh A, Tabibian S, Shams M, Tavasoli B, Gheidishahran M, Shamsizadeh M. Laboratory

Diagnosis of Factor XIII Deficiency in Developing Countries: An Iranian Experience. Lab Med. 2016

Aug;47(3):220-6