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Congenital Combined Bleeding Disorders, a Comprehensive Study of a Large Number of Iranian Patients

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Abstract

Congenital combined bleeding disorders (CBDs) are extremely rare disorders which mainly occur in regions with a high rate of consanguineous marriage. These disorders can present with a variety of symptoms ranging from mucocutaneous bleeding to life-threatening episodes. This study aims to evaluate the prevalence and clinical course of Iranian patients with congenital CBDs. This study is conducted on 450 patients with CBDs who were referred to the Iranian Comprehensive Hemophilia Care Center (ICHCC) between 2010 and 2020. All these patients were diagnosed through evaluation of past medical history and coagulation laboratory investigation. Out of 450 patients, 33 were entered in this study. Having excluded cases with factor (F) V and FVIII deficiency, as well as those with hereditary combined Vitamin K dependent clotting factor deficiency (VKCFD), We found the most common CBDs to be FV-FVII deficiency (n: 6, 18.1%), together with FVII and FX deficiency (n: 6, 18.1%). The most common reason for referral of these patients to ICHCC was postoperative bleeding (14.3%). The mean of The International Society on Thrombosis and Hemostasis-Bleeding Assessment Tool (ISTH-BAT) and condensed MCMDM-1VWD bleeding assessment tool were 9.6 $\pm$ 4.79 and 9.1 $\pm$ 4.87, respectively ($P < 0.005$). In 10 females of reproductive age, the mean of Pictorial Bleeding Assessment Chart (PBAC) score was 649.3 $\pm$ 554. Among all patients, 23 (69.7%) received on-demand replacement therapy, whereas 5 patients (15.1%) received prophylaxis. In Iran, the coinheritance of bleeding disorders is surprisingly higher than expected. Moreover, patients with congenital CBDs may experience serious bleeding manifestations.

Keywords

combined disorder, Iran, bleeding disorders

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Introduction

Congenital bleeding disorders are a heterogeneous group of disorders with an exceptionally rare prevalence far exceeding that of conventionally rare hemostatic disorders like factor (F) II or FXIII deficiencies.[1] Congenital bleeding disorders may present with a varied spectrum of clinical symptoms, ranging from mucocutaneous bleeding to life-threatening hemorrhage, such as bleeding in central nervous system (CNS), from the umbilical cord (UC), hemarthrosis, from gastrointestinal (GI) bleeding, and recurrent miscarriage.[2]

Among CBDs, there are 2 types of combined coagulopathies, including combined FV and FVIII deficiency (simultaneous decrease in the level of FV and FVIII) and combined vitamin K-dependent coagulation factors deficiency (VKCFD) defined as a concomitant decrease in the level of 4 (FII, FV, FVII, and FX) coagulation factor.[3] Quite apart from these uncommon disorders, there are also a very few cases of other combined coagulation factors deficiencies such as FV-FVII,

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FVII-FX, FVII-FIX, FVII-FVIII, FVII-FXI, and FVIII-FIX deficiencies which have been reported in a number of the publications.[1,4]

However, since studies describing such cases are sparse, we thought it useful to report 36 patients with a variety of extremely rare CBDs (other than FV-FVIII deficiency and VKCFD), referred to the Iranian Comprehensive Hemophilia Care Center (ICHCC).

Materials and Methods

Patients and Data Collection

In this study, 450 patients suffering from inherited combined hemostatic disorders and referred to ICHCC between 2010 and 2020, were evaluated. All patient data was retrieved from the clinical case notes, and the selected patients were all interviewed by our clinical staff. Patient data was recorded in a standard questionnaire focus on demographics information, result of laboratory investigation, clinical manifestations, the application of a condensed version of MCMD-1 VWD bleeding assessment tool, International Society on Thrombosis and Hemostasis-Bleeding Assessment Tool (ISTH-BAT), Pictorial Bleeding Assessment Chart (PBAC), and the management strategy adopted in these cases. Patients with FV-FVIII or VKCF deficiency were excluded from the study. Patients with an inherited combination of other bleeding disorders who had shown 2 successive abnormal coagulation laboratory investigations, after an interval of at least 6 months, with normal liver function tests and no other underlying clinical disorder, were included in the study. The medical ethics committee of ICHCC approved the study, and written consent was obtained from all patients or their parents, in the case of those under 18 years of age.

Laboratory Analysis

Following clinical assessment, all patients were referred to the ICHCC coagulation laboratory for the following assessemnet. Prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) which were determined using an automatic coagulometer (Sysmex CA 1500 coagulation analyzer, Dade Behring, Deerfield, IL, USA) with a normal range of 10 to 12 sec., 25 to 40 sec., and 15 to 19 sec., respectively. Bleeding time (BT) was determined using the Ivy method, as described by Nilsson et al.[5] Platelet counts were obtained from K2 Ethylenediaminetetraacetic acid (EDTA) blood samples (KX-21 hematology analyzer, Sysmex, Kobe, Japan). Coagulation factor activity was measured by 1-stage PT and PTT-based assays, using an automated coagulation analyzer (Sysmex CA 1500 coagulation analyzer, Dade Behring, Deerfield, IL, USA). In cases with low FV levels, FVIII levels were also measured to exclude combined FV-FVIII deficiency. Platelet function assays were performed within 4 hours from the time of blood collection. Following the preparation of platelet-rich plasma (PRP) and platelet-poor plasma (PPP), common agonists including ristocetin (0.75-1.50 mg/mL), ADP (200 μg/mL), collagen (200 μg/mL), and arachidonic acid (500 μg/mL) were added. The aggregometer was calibrated using autologous PPP (equivalent to 100% aggregation) and PRP (represents 0% aggregation). The aggregation tracing was observed for 5 to 10 minutes, to monitor the lag phase, shape change, primary, and secondary aggregation, and any delayed platelet responses.

VWF activity was evaluated with the VWF: ristocetin cofactor assay (VWF: RCo) by fixed platelet aggregometry using a PAP-4 (platelet Aggregation Profiler) Bio Data Corp. (Horsham, PA, USA). For VWF antigen (VWF: Ag) assessment, an immunological method (Siemens Healthcare Diagnostic Products, Marburg, Germany) was applied. Sodium dodecyl sulfate (1.3%) agarose gels electrophoresis and a modified visualization enzymatic method were used to analyze the VWF multimers.[6] Platelets CD surface markers expression was evaluated using FITC-conjugated antibodies against CD41, CD42, and CD61 (Becton-Dickinson, San Jose, USA) and analyzed using FlowJo software (Tree Star, Ashland, OR). In all cases, liver function tests (LFTs) including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALKP), and gamma-glutamyl transpeptidase (γ-GT) were performed with an autoanalyzer (Model BT3000, Biotechnica, Rome, Italy) to rule out acquired combined factor deficiency due to liver disease.

Results

Out of 450 patients diagnosed with different combined hemostatic disorders, 233 cases had VKCFD (in either hereditary or acquired form), 162 cases had FV-FVIII deficiency, 9 cases had acquired deficiency of at least 1 coagulation factor. Finally, 46 cases with inherited CBDs were recognized. Eleven patients were excluded from the study due to the availability of only 1 laboratory test result. Furthemore, 2 patients with combined afibrinogenemia and FV-leiden were also excluded Among the remaining 33 patients, 18 (54.6%) were male, and 15 (45.4%) were female. The mean age of the selected cohort of patients was 21.8 $\pm$ 14.81 years of age. The mean age at diagnosis was 14 $\pm$ 14.66. The most common CBDs were FVII and FX deficiency and FV and FX deficiency (n: 6, 18.1%) (Table 1).

Discussion

CBDs are a heterogeneous group of inherited hemorrhagic disorders with varying clinical features and laboratory findings, which have mostly been reported from regions with a high rate of parental consanguinity. CBDs are extremely rare disorders which include 2 distinct types, including FV-FVIII deficiency, and VKCFD.[7] However, there are a number of reports of other multiple CBDs. This study has evaluated 35 cases of CBDs other than combined FV-FVIII and VKCF deficiency.

We describe a total 19 cases (51.4%) of combined FVII deficiency with other bleeding disorders including FVII and afibrinogenemia (15.7%), FVII-FV (31.5%), FVII-FX (31.5%), FVII-FXI (5.3%), and FVII-FXIII (5.3%) deficiencies, as well as FVII-hemophilia B (HB) (5.3%), and

Table 1. Demographic Characteristics and Laboratory Results of Patients With Congenital Combined Bleeding Disorders.

N	Sex	Age (Year)	Age of diagnosis (Year)	Disorder	First laboratory assays*	Reason of diagnosis	Other clinical manifestation	BAT score	MCMDI score	PBAC score	Type of treatment	Parental consanguinity	Family history **
1	F	42	38	FXID + Low VWF	FXI: C: 6% FVIII: C: 36% VWF:RCo: 33% VWF:Ag: 35%	Pre-operative tests	Epistaxis Bruising Delayed wound healing Menorrhagia	10	8	884	Haemate® (*CSL Behring, Marburg, Germany*), TXA (OD)	Neg	Neg
2	F	31	21	FXID + Type I VWD	FXI: C: 35% FVIII:C: 32%VWF:RCo: 20% VWF:Ag: 29%	Post-dental extraction bleeding	Oral cavity bleeding Post-surgery bleeding	8	8	295	TXA (OD)	Neg	Neg
3	M	27	6	FXID+ Low VWF	FXI:C: 28% VWF:RCo: 33% VWF: Ag: 35%	Post-dental extraction bleeding	Epistaxis Delayed wound healing Hematuria	7	6	–	Haemate® (*CSL Behring, Marburg, Germany*) (OD)	Neg	Neg
4	M	46	38	FV-FVII	FV: C: 32% FVII: C : 31%	Positive family history	Oral cavity bleeding Post-dental extraction bleeding Hemarthrosis	8	8	–	rFVII (AryoSevenTM, Aryogene, Iran) (OD)	Pos	Pos Son (#4 and #5)
5	M	5	2	FV-FVII	FV: C: 39% FVII: C : 24%	Positive family history	Post circumcision bleeding	9	9	–	rFVII (AryoSeven™, Aryogene, Iran) (OD)	Pos	Pos Brother (#4) Father (#6)
6	M	20	1	FV-FVII	FV: 3% FVII: <1%	Epistaxis	Epistaxis Bruising Post-dental extraction bleeding Hemarthrosis	15	15	–	rFVII (AryoSeven™, Aryogene, Iran) (OD)	Pos	Pos Brother (#5) Father (#6)
7	F	1	1 Mo	FVII-FXIIID	FVII: 26% FXIII: <29 min	Umbilical cord bleeding	Delayed wound healing Bruising Hematoma	11	5		*Corifact™/Fibrogammin®* 250 IU/once a month	Pos	Neg
8	F	30	14	FXI-FXIID	FXI:C: 35% FXII:C: 30%	Epistaxis	Delayed wound healing Epistaxis Gum bleeding	5	5	–	None	Pos	Neg
9	F	2	1 Mo	FV-FIXD	FV: <1% FIX: 31%	Umbilical cord bleeding GI bleeding	Gum bleeding Hematoma	13	11	–	FFP (PRO)(every 2 weeks)	Neg	Neg
10	M	28	20	FV-FXID	FV: 25% FXI: 25%	Epistaxis	Delayed wound healing	8	7	–	TXA(OD)	Neg	Neg
11	M	4	5 Mo	FID+BSS	FI: 0.31% CD41: 97.4% CD42: 1.4%, CD61: 98.4%Platelet: 104 × $10^3/\mu l$	Hematuria	Ecchymosis Bruising Gum bleeding-Epistaxis	12	12	–	Cryo (OD) Platelet (OD)	Neg	Neg
12	M	18	NA	FV-FVII	FV: 38% FVII: 40%	Gum bleeding	Epistaxis Ecchymosis	5	5	–	OD*	Pos	Neg
13	M	23	7	FVII-FIXD	FVII: 28% FIX: 1.5%	Post-dental extraction bleeding	Gum bleeding-Epistaxis Ecchymosis	4	3	–	FIX (OD)	Neg	Neg

(continued)

Table 1. (continued)

N	Sex	Age (Year)	Age of diagnosis (Year)	Disorder	First laboratory assays*	Reason of diagnosis	Other clinical manifestation	BAT score	MCMDI score	PBAC score	Type of treatment	Parental consanguinity	Family history **
14	M	21	16	FVII-FXID	FVII: 30% FXI: 32%	Menorrhagia	Menorrhagia-Ecchymosis Delayed wound healing Oral cavity bleeding Post-dental extraction bleeding	21	21	2090	On-demand	Neg	Pos
15	M	38	NA	HA-HB	FVIII: C: 42% FIX: C: 22%	Gum bleeding	Hematoma Post-dental extraction bleeding Epistaxis Bruising GI bleeding Gum bleeding Hemarthrosis	20	20	–	FIX (OD) TXA(OD)	Neg	Neg
16	M	18	7	HA-HB	FVIII: C: 23% FIX: C: 33%	Post-operative bleeding	Epistaxis Ecchymosis Delayed wound healing Post dental extraction bleeding Post-operative bleeding Hemarthrosis	19	19	–	FFP (OD)	Pos	Neg
17	M	32	NA	HA-FXID	FVIII:34% FXI: 42%	Epistaxis	Bruising Gum bleeding Hemarthrosis	12	12		On-demand	Pos	Pos
18	F	4	1	HA-FXID	FVIII: 31% FXI: 37%	Hematoma	None	4	4	–	On-demand	Neg	Neg
19	F	40	28	HA-FXID	FVIII: 25% FXI: 28%	Prolonged PTT	Ecchymosis Post-dental extraction bleeding Post-partum hemorrhage Menorrhagia	9	9	390	FFP (OD)	Neg	Pos Brother have FXI deficiency
20	F	9	9	FI-FVIID	FI: 0.4% FVII: 36%	Bruising	Delayed wound healing	4	4	–	None	Pos	Neg
21	F	54	50	FI-FVIID	FI: 0.61% FVII: 39%	Menorrhagia	Gum bleeding Epistaxis Ecchymosis	11	11	650	Fibrinogen (OD)	Neg	Pos Son with FVIID
22	F	30	29	FV-FVII	FV:40% FVII: 13%	Pre-operative screening	Bruising Delayed wound healing Oral cavity bleeding Post-surgery bleeding	9	8	326	FFP (OD)	Pos	Neg
23	F	17	1	FI-FVIID	FI: <0.2% FVII: 37%	Intracerebral hemorrhage	Bruising Delayed wound healing Menorrhagia	10	9	709	Fibrinogen (PRO-every 10 days 1gr)	Pos	Neg

(continued)

Table 1. (continued)

N	Sex	Age (Year)	Age of diagnosis (Year)	Disorder	First laboratory assays*	Reason of diagnosis	Other clinical manifestation	BAT score	MCMD1score	PBAC score	Type of treatment	Parental consanguinity	Family history **
24	F	11	10	FVII-FXD	FVII: C: 20% FX: C: 35%	Family history	Epistaxis Bruising	5	5	–	None	Pos	Pos Brother (#25 and #26) Father (#31)
25	M	5	4	FVII-FXD	FVII: C: 18% FX: C: 10%	Family history	Asymptomatic	0	0	–	None	Pos	Pos Brother (#24) Father (#27) Sister (#24)
26	M	13	12	FVII-FXD	FVII: C: 19% FX: C: 37%	Family history	Post-dental extraction bleeding	4	4	–	None	Pos	Pos Brother (#25) Father (#27) Sister (#24)
27	M	41	36	FVII-FXD	FVII: C: <1% FX: C: 15%	Gum bleeding	Epistaxis	13	13	–	rFVII (AryoSevenTM, Aryogene, Iran) (OD)	Pos	Pos Son Daughter
28	F	19	NA	FVII-FXD	FVII: C: 22% FX: C: 37%	Prolonged PT and PTT	Post-operative bleeding Gum bleeding Delayed wound healing	7	7	110	FFP(OD)	Neg	Neg
29	M***	4	2 months	FVII-FXD	FVII: C: <1% FX: C: 30%	CNS Bleeding	Ecchymosis GI bleeding Hematoma CNS bleeding	15	15		rFVII (AryoSevenTM, Aryogene, Iran) (OD)	Pos	Neg
30	M	39	27	FVIID+ Low VWF	FVII:C: 33% FVIII:C: 38%VWF:RCo: 30% VWF: Ag: 35%	Bruising	Gum bleeding – Epistaxis Post dental extraction bleeding	10	10	–	rFVII (AryoSevenTM, Aryogene, Iran) (OD)	Neg	Neg
31	M	14	NA	FXID+ Type II M vWD **** p.Arg1379Cys (c.4135C>T) (7)	FXI: 10% FVIII: 15%vWF activity (Ricof): 28% vWF Ag: 59%	Post-operative bleeding	Oral cavity bleeding Epistaxis Bruising	12	11	–	Haemate® (*CSL Behring*, Marburg, *Germany*) (OD)	Neg	Neg
32	F	46	44	FXID+ Low VWF	FXI: 5% FVIII:51%vWF activity (Ricof): 39% vWF Ag: 31%	Bruising	Menorrhagia	11	10	575	On-demand	Neg	Neg
33	F	38	34	FV-FVIID	FV:16% FVII:32%	Menorrhagia	Oral cavity bleeding	9	9	464	TXA (OD)	Neg	Neg

F: Female, M: Male, LMWH: Low Molecular Weight Heparin, OD: on-demand, Pro: Prophylaxis, FFP: Fresh Frozen Plasma, TXA: tranexamic acid, CNS: central nervous bleeding, PTT: partial thromboplastin time, Pos: positive, Neg: negative, NA: not available.

*The normal ranges for laboratory assays are as follow: Fibrinogen: 1.5-4.5 g/dL, FV, FVII, FVIII, FIX, FX and FXI plasma level: 50-150%, VWF:Ag and VWF:RCO: 50-150%, platelet count: 150-450.

*The number in parenthesis is the patient number with same bleeding disorder.

**The FVII inhibitor titer is 14.7 and he died due to an extensive intracerebral hemorrhage.

**** The multimers pattern was normal. Forty-eight percent of the patients were the progeny of consanguinous marriages. A positive family history of bleeding was obtained from 11 patients (33.3%). The commonest reason for referral of these patients to ICHCC was a positive family history (15.1%) followed by epistaxis (12.1%) (Figure 1). Four patients were diagnosed because of a positive family history of bleeding. Life-threatening bleeding episodes including CNS bleeding (#23, 29), GI bleeding (#9), UC bleeding (#7,9), and miscarriage (#7,8) result in the diagnosis of 6 patients (18.1%). No life-threatening bleeding episodes were observed in the remaining patients (81.9%). The mean of ISTH-BAT and MCMD1 scores were 9.6 $\pm$ 4.79 and 9.1 $\pm$ 4.87, respectively (Table 2). Compared to the MCMD1 score, the mean ISTH-BAT score was higher ($P < 0.005$). In female of menstrual age, the mean of PBAC score was 649.3 $\pm$ 554. Among these patients, menorrhagia was the main reason for their referral, in only 3 cases. Twenty-three (69.7%) received on-demand treatment, whereas 5 patients (15.1%) were put on prophylactic treatment.

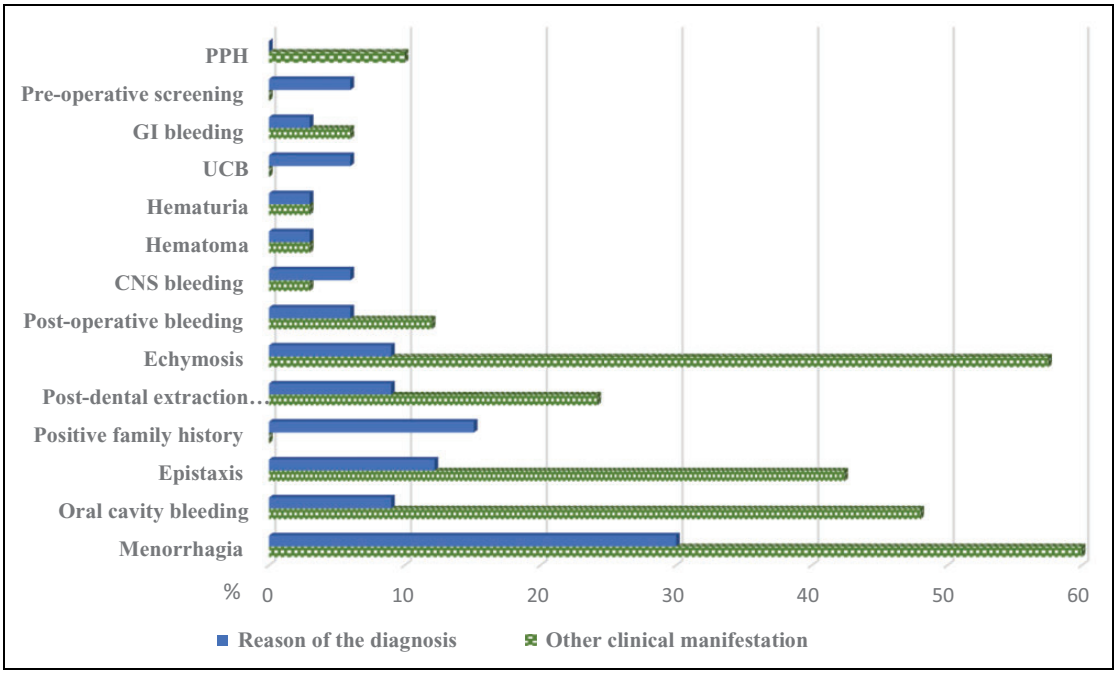

Figure 1. Distribution of clinical manifestations in patients with combined bleeding disorders. PPH: Postpartum hemorrhage, GI bleeding: Gastrointestinal bleeding; UCB: Umbilical cord bleeding; CNS: Central nervous bleeding. Menorrhagia and PPH were estimated among the female of reproductive age.

Table 2. Demographic and Clinical Information of the Patients with Congenital Combined Hemostatic Disorders.

Population	Mean Age (year)	Mean age of the diagnosis (year)	Mean ISTH-BAT score	Mean MCMD1 score	The most common clinical manifestation	The most common combined diosrders
Male	22 ± 13	12.9 ± 12.7	10.4 ± 6.1	10.5 ± 5.9	Echymosis	FV-FVII deficiency (26.6%) FVII-FX deficiency (26.6%)
Female	26.6 ± 16.49	21.4 ± 17	8.8 ± 2.9	7.5 ± 2.2	Echymosis	FXI deficiency-Low VWF (13.3%) FV-FVII deficiency (13.3%) FVII-FX deficiency (13.3%)
Total	21.8 ± 14.81	14 ± 14.66.	9.6 ± 4.79	9.1 ± 4.87	Echymosis	FVII-FX deficiency (18.1%) FV-FVII deficiency (18.1%)

FVII-type I VWD (5.3%). There are various reports in the literature, reporting combined deficiency of FVII with FI, FV, FVIII, FIX, FX, FXI, and FXIII deficiencies.[1,8-13]

We identified a 1-year-old girl with combined FVII-FXIII deficiency, whose most salient complication was UC bleeding, just like patients with severe FXIII deficiency alone.[14,15] Concomitant deficiency of FVII and FXIII is very rare and has only been reported in a single, male patient from Sistan and Baluchistan province in the south-eastern of Iran.[1] This patient was actually born in neighboring Kerman province.

We also report 6 cases of combined FVII and FX deficiency, where 4 of them were members of the same family. A further case is a 2-month old FVII deficient boy who developed a FVII inhibitor after rFVIIa therapy-a very uncommon complication, who later died due to an extensive intracranial hemorrhage (ICH). According to the comprehensive study of Girolami et al. on the combination of FX deficiency with other coagulopathies, the most frequent type was with FVII deficiency.[15] In our study, the commonest CBDs was FVII-FX deficiency. Furthermore, in 2004, Menegatti et al reported 2 Iranian siblings, who were the progeny of a a consanguineous marriage, and were affected with FVII and FX deficiency.[16,17] An intriguing report by F.Zheng et al. encountered a 16-year-old Chinese boy without any history of bleeding diathesis, who had accidentally ingested a diphacinone rodenticide, which interferes with the synthesis of vitamin K-dependent coagulation factors. The patient received a vitamin K_1 injection, but his PT and APTT tests remained prolonged. After evaluation of FVII and FX activity together with molecular analysis, the patient was found to suffer from congenital combined FVII and

FX.[18] The genes encoding FVII and FX are located on chromosome 13 (13q34), and combined FVII-FX deficiency is also reported in several cases with 13q34 deletion syndrome.[19-21] We also reported 3 females with combined afibrinogenemia and FVII deficiency, who were investigated due to ICH, menorrhagia, and bruising, respectively. To our knowledge, there is only 1 similar, previous report of heterozygous dysfibrinogenemia and FVII deficiency. The patient in question was a 51-years-old man fortuitously diagnosed after pre-operative screening tests.[22] We have also identified 6 cases with congenital coagulopathies due to FVII and FXI deficiency, associated with VWD, where 5 of them were affected by FXI deficiency, together with either type I VWD, or low VWF. The prevalence of congenital, combined coagulopathies, and VWD is not common in the medical literature, and their management appears to be challenging. A thorough study by Asatiani et al. on VWD combined with HA, HB, FVII, XI, or XII deficiency, reported a wide range of clinical complications. Combined type I VWD and FXI deficiency presented with bleeding episodes typical of type I VWD, while the combination of type I and IIN VWD with FVII deficiency caused severe bleeding diathesis.[23] Two cases with combined HA and HB were identified in our study. Both were affected by clinically mild HA and HB. However, the ISTH-BAT score were 19 and 20. Previously, 2 separate cases were reported by Shetty et al. and Naderi et al. in 2001 and 2015, respectively.1,4 The former instance occurred in an Indian family, and the latter case was a 1 month-old boy from southeast of Iran, who developed bleeding after circumcision leading to a diagnosis of combined HA and HB. In 2016 Ivaškevičius et al. reported a case of HB which failed to respond to plasma-derived FIX concentrate prior to dental extraction, resulting in persistent bleeding. Further evaluation revealed a diagnosis of combined HA and HB deficiency at the unexpectedly advanced age of 42.[24] We also found 3 cases of combined HA and HB deficiency. There are very few instances reported of this combined coagulopathy.[25-27] In our study, we identified 1 case of combined FXI and FXII deficiency with a mild to moderate bleeding phenotype. Since FXII deficiency is not associated with bleeding tendency, episodes of hemorrhage must be attributed to the FXI deficiency.

For the first time, we have identified a patient with combined afibrinogenemia and bernard soulier syndrome (BSS), who was diagnosed early in her life, due to hematuria. Other studies have reported the co-expression of deficiencies of prekallikrein, FXI, and FXII with BSS.[28-30]

All these findings indicate that the co-inheritance of hemostatic disorders in Iran is surprisingly greater than expected. All patients with congenital hemostatic disorders should be thoroughly evaluated, considering the patient's phenotype and genotype, the personal and family medical history, together with the degree of consanguinity, in order to prevent misdiagnosis, and provide for proper care and management.

Declaration of Conflicting Interests

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