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ORIGINAL ARTICLE

Rare Bleeding Disorder Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias

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Summary. A North American registry for rare bleeding disorders [factor (F)II, factor (F)VII, factor (F)X, factor (F)V, factor (F)XIII, fibrinogen deficiencies and dysfibrinogenemias] was established to gather information about disease prevalence, genotyping frequency, diagnostic events, clinical manifestations, treatment and prophylaxis strategies, as well as disease- and treatment-related complications. Questionnaires were sent to 225 hemophilia treatment centers in the USA and Canada. Among 26% of responding centers, 294 individuals [4.4% of the registered children (200/4583) and 2.4% of adults (94/3809)] were diagnosed with one or more of the rare bleeding disorders (RBDs) included in this survey. The ethnic distribution for each disorder paralleled that of the general US population with the exception of the disproportionately large number of Latinos with FII deficiency. Only 5.4% of affected individuals were genotyped. An abnormal preoperative bleeding screen most often led to diagnosis. The most common coagulopathy was FVII deficiency; however, 40% of homozygous patients were asymptomatic. FX and FXIII deficiencies caused the most severe bleeding manifestations. Among all RBDs, the most common sites of bleeding were skin and mucus membranes. Multiple products were used to treat hemorrhage; however, half of the bleeding episodes required no therapy. The majority of patients suffered no long-term complications from hemorrhage. Treatment-related complications included viral seroconversion, anemia, allergic reactions and venous access device-related events. This registry provides the most comprehensive information to date about North American individuals with RBDs and could serve as an important resource for both basic scientist and clinician.

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Introduction

Rare inherited bleeding disorders [factor (F)II, factor (F)VII, factor (F)X, factor (F)V, factor (F)XIII deficiencies, fibrinogen and dysfibrinogenemias] constitute an important group of coagulopathies. Von Willebrand disease, hemophilia A, B and factor XI deficiency are the most frequent congenital bleeding disorders with general population prevalence rates of between 1 and 0.001% [1,2]. However, rare bleeding disorders (RBDs), largely inherited by autosomal recessive genetics, occur with an estimated prevalence of between 1 and 2 per 10^6 individuals [3]. Consequently, when compared with the common bleeding disorders, most RBDs are not as well characterized clinically and do not have well-established treatment strategies. In the last decade, progress has been made in understanding the genetic basis of most RBDs [4–10]. This development increases the potential for genotype/phenotype correlation, and consequent optimization of management strategies.

Because there are few published large cohort studies of these patients, we established The North American Registry of Rare Bleeding Disorders. The registry's main objectives were to: (i) gather epidemiological data on disease prevalence, diagnosis and genotypic characterization; (ii) characterize type and severity of bleeding manifestations; (iii) understand current treatment strategies in the USA and Canada; and (iv) document complications of the underlying disorder and its treatment. In collaboration with the Haemophilia Research Society, we also set out to develop a RBDs database intended to facilitate the further study of gene-based diagnosis, genotype–phenotype correlation and new treatment strategies.

Materials and methods

Data were collected between March and December 1999 by questionnaire mailed to 225 registered hemophilia treatment

centers (HTCs) in the USA and Canada. Since all information was anonymously collected (no individual patient identifiers), neither informed consent nor formal ethics committee approval was then required. The data collection instrument gathered the following: (i) disease prevalence, (ii) current age and age at diagnosis, (iii) family history of disease (positive family history), (iv) genotype information, (v) clinical manifestations (including bleeding sites, triggers and frequency), (vi) treatment strategies, and (vii) complications of disease and/or its therapy. Bleeding events and treatment had to be documented in hospital records to qualify for inclusion. FII, FVII, FX and FV deficiency individuals were classified as homozygous (more severely affected) or heterozygous based on factor activity levels either less than or $\geq 0.2\,\mathrm{U\,mL^{-1}}$, respectively [10,11]. The classification was based on the fact that hemostatic levels for most of these factors are in the $0.1–0.15\,\mathrm{U\,mL^{-1}}$ activity range and hence $0.2\,\mathrm{U\,mL^{-1}}$ was chosen as a cut-off. Also, clotting factor antigen and/or activities $<0.2\,\mathrm{U\,mL^{-1}}$ were reliably reflected by marked prolongations of the prothrombin time (PT)/partial thromboplastin time (PTT) to be able to differentiate symptomatic vs. the carrier state. Similarly individuals with fibrinogen disorders were also classified as homozygous (activity $<50\,\mathrm{mg\,dL^{-1}}$) or heterozygous (activity between $50\,\mathrm{mg\,dL^{-1}}$ and upper limit of normal range for local laboratory). FXIII deficiency was always considered to be homozygous. Dysfibrinogenemia was considered to be heterozygous. Factor antigen levels were requested to determine the relative prevalence of qualitative and quantitative disorders. As this was a descriptive database, statistical analysis was performed only for ethnic prevalence using the χ^2 goodness of fit test (GOF); $P < 0.01$ was chosen as the level of significance.

Results

Demographics/gene mutation analyses

The 58 responding centers (26%) treated a total of 3809 adults and 4583 children with hemorrhagic disorders, of whom 2.4% (94/3809) adults and 4.4% (200/4583) children (age 0–18 years) were diagnosed as having at least one RBD surveyed. Unfortunately, gender information was not requested. Age at diagnosis ranged from birth to 73 years (median of 7 years); 50% had one or more affected family members. Gene mutation analysis had been performed in only 16 (5.4%) affected families: FVII ($n = 8$), FV ($n = 5$), FXIII ($n = 2$) and afibrinogenemia [1].

Epidemiology

The frequency distribution of these disorders in this database is depicted in Fig. 1. The most common disorder was FVII deficiency (46% of all RBDs). Combined congenital deficiencies were noted in nine patients (3%). Of these, seven were diagnosed with FVII deficiency in combination with FV ($n = 3$), FX ($n = 3$), or FII ($n = 1$). One individual had combined factor VIII and FV deficiency; another had combined congenital deficiencies of FV, FVII and FX.

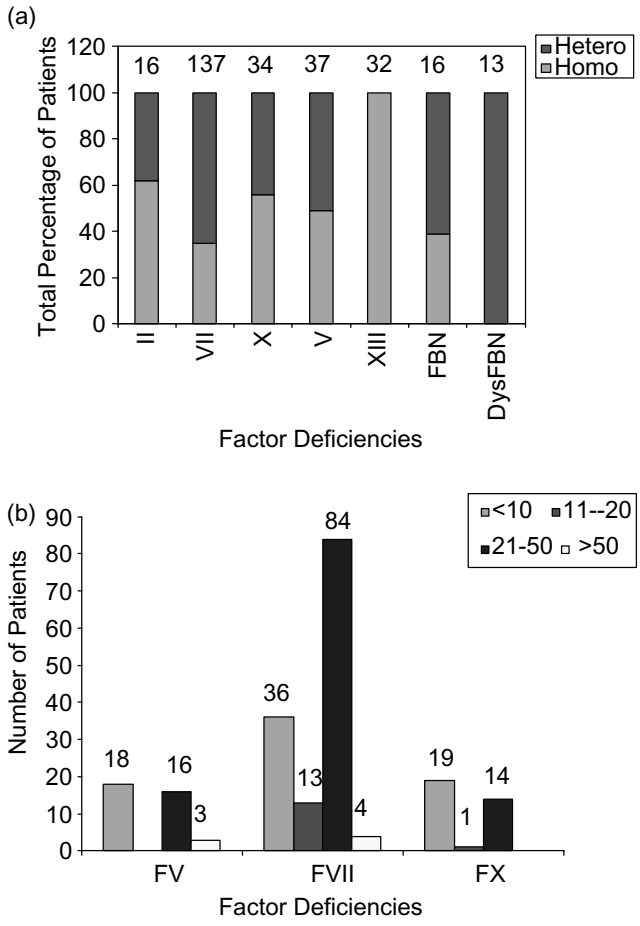

Fig. 1. (a) Factor distribution by frequency and activity levels. Frequency distribution of rare factor deficiencies (numbers of patients). FBN, Fibrinogen disorders; DysFBN, dysfibrinogenemia; Homo, homozygous; Hetero, heterozygous. Homozygous and heterozygous for factors II, VII, X, V defined as activity <20% or ≥20%, respectively; factor XIII considered to be homozygous and dysfibrinogenemias considered heterozygous; homozygous for fibrinogen disorders defined as fibrinogen levels $<50\,\mathrm{mg\,dL^{-1}}$; heterozygous defined as activity between $50\,\mathrm{mg\,dL^{-1}}$ and upper limit of normal range for local laboratory. (b) Factor distribution levels. Factor activity levels for homozygous and heterozygous patients with factors V, VII, X deficiency using $0.2\,\mathrm{U\,mL^{-1}}$ as the cut-off.

The relative prevalence of homozygosity and heterozygosity for each disorder is depicted in Fig. 1a. Between 35% (FVII) and 62% (FII) of individuals were classified as homozygous. Twenty-four percent of those with all fibrinogen disorders had afibrinogenemia. Unfortunately, there was insufficient information on factor antigen levels to ascertain the relative prevalence of dysproteinemia.

The majority of RBD individuals were Caucasian, except for FII deficiency (62% Latinos) (Table 1). A χ^2 GOF test was performed using four ethnic groups (Caucasians, African-American, Latino, and Asian/others, the last two groups combined due to small expected cell frequencies). The GOF test showed that the observed ethnic distribution differed

Table 1 Race distribution (%) for each factor deficiency (across) and for all rare bleeding disorders (RBDs) (averaged per race) compared with US census data for race (down)

	Caucasian (%)	African-American (%)	Latino (%)	Asian (%)	Others (%)
Factor II	25	0	62	0	12
Factor VII	57	23	13	3	4
Factor X	57	17	20	0	5
Factor V	67	5	20	2	5
Factor XIII	62	6	19	3	9
Fibrinogen disorders	75	19	0	0	6
Dysfibrinogenemias	85	0	0	8	7
% US Population	76	12	**8.2**	3	0.8
% all RBDs	61	13	**19**	2	5

Others, Mixed races.

significantly from the US population ($P < 0.0001$) for Latinos and others who were clearly over-represented.

Diagnostic events, hemorrhagic manifestations and treatment strategies

The circumstances leading to diagnosis, the hemorrhagic manifestations of disease and the strategies used to treat or prevent bleeding are discussed separately for homozygous and heterozygous subjects with each surveyed factor deficiency. Insufficient information was received to assess bleeding frequency for any disorder.

FII deficiency

Homozygous subjects Ten subjects (62% of cohort) were homozygous. The median FII activity was $0.03\,U\,mL^{-1}$ (range <0.01–0.18). Hemorrhage (60%) or a positive family history (40%) led to diagnosis in all cases. All subjects had bleeding manifestations involving skin and mucus membranes (40% of all events), joints and muscles (26%), gastrointestinal and genitourinary tracts (13% each) and the cranium (8%). Of those with FII $<0.01\,U\,mL^{-1}$, 20% had intracranial bleeds. Sixty percent of bleeding was unprovoked; 40% was trauma induced. Most (98%) required treatment using activated (APCCs) or non-activated prothrombin complex concentrates (PCCs) (45% of replacement therapy), fresh frozen plasma (FFP) (29%), or epsilon amino caproic acid (EACA) alone (24%). Prophylaxis was not reported (Table 2a).

Heterozygous subjects Six subjects (38% of cohort) were heterozygous with a median FII activity of $0.25\,U\,mL^{-1}$ (range 0.21–0.35). Diagnosis was made following hemorrhage in 67% and abnormal preoperative lab screening in 33% of individuals. Eighty-three percent experienced bleeding, all in the skin and mucus membranes. Bleeding episodes were predominantly spontaneous (60%) and less often trauma induced (40%). Forty-nine percent of hemorrhage required therapy with PCCs/APCCs (33%) or FFP (16%) (Table 2b).

FVII deficiency

Homozygous subjects Forty-nine subjects (36% of cohort) were homozygous with a median FVII activity of $0.08\,U\,mL^{-1}$ (range <0.01–0.18). Diagnostic events included abnormal PT (40% of individuals), history of bleeding (40%), positive family history (12%), postoperative hemorrhage (6%), and venous thromboembolism (2%). Among the 54% who bled, hemorrhage was skin and mucus membrane-related (60% of episodes), musculoskeletal (21%), gastrointestinal (16%) or genitourinary (3%). Bleeding was largely spontaneous (84%) and less commonly trauma or alcohol-related (16%). Seventy-three percent of bleeding events were successfully treated with FFP (35% of episodes), FVII concentrate (including activated FVII) or PCCs (14% each) or EACA (10%, mucus membrane bleeds). Uniformly good hemostasis was achieved with initial choice of therapy. For prophylaxis, FFP (28%), PCCs (29%), FVII concentrates (29%) and EACA alone (15%, for dental procedures) were used (Table 2a).

Heterozygous subjects The 88 heterozygous subjects (64% of cohort) had median plasma FVII activity of $0.35\,U\,mL^{-1}$ (range 0.21–0.69). An abnormal preoperative PT most often precipitated the diagnosis (55%), followed in frequency by non-surgical hemorrhage (23%), positive family history (19%), prolonged postoperative bleeding (2%), and thromboembolism (1%). Among the 36% with hemorrhage, skin and mucus membrane bleeding predominated (76%), followed by gastrointestinal (11%), musculoskeletal (7%), intracranial (4%) and genitourinary (2%) bleeding. Most was spontaneous (61%). Forty-four percent of events required therapy with FFP (26%) cryoprecipitate, recombinant activated FVII (rFVIIa), and EACA alone (5–8% each). Surgical prophylaxis was performed with rFVIIa (36%), FFP (27%), EACA (27%), and PCCs ([10%) (Table 2b).

FX deficiency

Homozygous subjects Nineteen subjects (56% of cohort) were homozygous, with a median FX plasma activity of $<0.01\,U\,mL^{-1}$ (range <0.01–0.13). Non-surgical bleeding (82%) was the most common diagnostic event, followed by positive family history (14%) and postoperative bleeding (4%). All had bleeding symptoms, predominantly in the skin and mucus membranes (45%), followed by musculoskeletal (27%), intracranial (15%), gastrointestinal and genitourinary (4–9%) hemorrhage. Of patients with intracranial bleeds, 53% had a FX activity of $<0.01\,U\,mL^{-1}$. Bleeding triggers were absent (80%) or traumatic (15%). Inadequate information was provided for 5% of events. PCCs (46%) and FFP [including solvent detergent FFP (SD FFP) (39%)] were used to treat 96% of events. FFP (50%) and PCCs and EACA alone (25% each) were administered for surgical prophylaxis (Table 2a).

Table 2a Products used for treatment and prophylaxis in homozygous deficiency

	II	VII	X	V	XIII	Afibrinogenemia
Treatment (% of all bleeding episodes for each deficiency)						
Fresh frozen plasma	29	35	39	93	45	10
(A)PCCs	45	14	46	5	0	0
Concentrates	0	14	0	0	24	10
Cryoprecipitate	0	0	8	0	24	50
EACA	24	10	7	0	6	30
None	2	27	4	0	1	0
No information	0	0	0	1	0	0
Prophylaxis (% of surgical and dental procedures with prophylaxis)						
Fresh frozen plasma	0	28	50	0	66 ($n=2$)	0
(A)PCCs	0	29	25	0	0	0
Concentrates	0	29	0	0	0	0
Cryoprecipitate	0	0	0	0	0	0
EACA	0	15	25	0	0	0

(A)PCCs, Activated prothrombin complex concentrates; Concentrates, factor concentrates; EACA, epsilon amino caproic acid.

Table 2b Products used for treatment and prophylaxis in heterozygous deficiency

	II	VII	X	V	Hypo-fibrinogenemias	Dys-fibrinogenemias
Treatment (percent of all bleeding episodes)						
Fresh frozen plasma	16	26	12	30	100 ($n=1$)	0
(A)PCCs	33	0	12	0	0	0
Concentrates	0	5	0	0	17	0
Cryoprecipitate	0	5	0	0	33	38
EACA	0	8	12	50	0	0
None	51	56	64	20	8	50
No information	0	0	0	0	42	12
Prophylaxis (percent of surgical and dental procedures using prophylaxis)						
Fresh frozen plasma	0	27	33	0	0	0
(A)PCCs	0	10	33	0	0	0
Concentrates	0	36	0	0	0	0
Cryoprecipitate	0	0	0	0	0	100 ($n=1$)
EACA	0	27	34	0	0	0

(A)PCCs, Activated prothrombin complex concentrates; Concentrates, factor concentrates; EACA, epsilon amino caproic acid.

Heterozygous subjects Fifteen subjects (44% of cohort) were heterozygous, with a median FX activity of $0.38\,U\,mL^{-1}$ (range 0.23–0.47). The diagnostic trigger was usually a positive family history (47%) or an abnormal preoperative laboratory screen (47%), with prediagnostic bleeding being uncommon (6%). A negative bleeding history was noted in 67% of diagnosed patients. Among the symptomatic 33%, skin and mucus membrane bleeding predominated (75%), followed by gastrointestinal (12%) and postoperative hemorrhage (13%). Insufficient information on bleeding triggers was obtained. Sixty-four percent of bleeding events were not treated. FFP, PCCs, and EACA were used to treat the other episodes (12% each) and for prophylaxis (one-third each) (Table 2b).

FV deficiency

Homozygous subjects Eighteen subjects (49% of cohort) who were homozygous had a median FV activity of $<0.01\,U\,mL^{-1}$ (range <0.01–0.05). Bleeding (76%), positive family history (18%) or an abnormal preoperative laboratory screen (6%) led to diagnosis. All ultimately experienced bleeding, mainly into the skin and mucus membranes (44%), joints and muscles (23%), as well as genitourinary (19%) and gastrointestinal tracts (6%). Intracranial hemorrhage represented 8% of bleeding; 25% of these events were associated with a FV activity of $<0.01\,U\,mL^{-1}$. All bleeding events were spontaneous and 99% were treated with FFP (93%) or PCCs (6%). No prophylaxis was reported (Table 2a).

Heterozygous subjects Nineteen subjects (51% of cohort) were heterozygous with a median FV activity of $0.35\,U\,mL^{-1}$ (range 0.21–0.55). Diagnostic events included positive family history (44%), abnormal preoperative laboratory screen (39%) and hemorrhage (17%). In the symptomatic 50% of individuals, skin and mucus membrane bleeding predominated (62%). Musculoskeletal (19%), and genitourinary (19%) bleeding accounted for the rest. All bleeding events were spontaneous. Hemostasis therapy included FFP (30%) and EACA alone (50%) (Table 2b).

FXIII deficiency

Thirty-two subjects had FXIII deficiency. Diagnostic events included non-surgical (46%) or postoperative (6%) hemorrhage and a positive family history (31%), with no reported information (17%). Bleeding occurred predominantly in skin and mucus membranes (47% of which 22% were umbilical stump bleeding), followed by joints and muscles (27%), cranium (10%), genitourinary tract (9%), surgical wounds (4%) and gastrointestinal tract (3%). Hemorrhage was mostly spontaneous (71%), with no reported information in 13%. Ninety-nine percent of bleeding episodes were treated using FFP/SD FFP (45%), cryoprecipitate (24%), investigational FXIII concentrate (24%), and EACA (6%). Eleven patients (34%) were on long-term prophylaxis with FXIII concentrate. Surgical prophylaxis was performed with FFP ($n = 2$) and cryoprecipitate ($n = 1$) (Table 2a).

Fibrinogen disorders

Afibrinogenemia Seven subjects (24%) with fibrinogen disorders had afibrinogenemia (activity $<50\,\text{mg dL}^{-1}$). Diagnostic events included non-surgical (43%) or postoperative bleeding (14%) and positive family history (43%). All patients experienced bleeding, mainly into skin and mucus membranes (49%), followed by genitourinary (18%), musculoskeletal (26%), cranial (5%) and gastrointestinal (2%) hemorrhage. Unlike with most other severe deficiencies, afibrinogenemia-related events were triggered mainly by trauma (71%); only 28% occurred spontaneously. All bleeding events were treated with cryoprecipitate (50%), EACA alone (30%), investigational fibrinogen concentrate (10%) or FFP (10%) (Table 2a). No prophylaxis was reported.

Hypofibrinogenemia Eleven subjects (38%) with fibrinogen disorders had hypofibrinogenemia [median level $68\,\text{mg dL}^{-1}$ (range 51–117)]. Diagnostic events included non-surgical bleeding (46%), positive family history (36%), and postoperative bleeding (18%). Among the symptomatic patients (73% of cohort), bleeding occurred in skin and mucus membranes (45%), joints and muscles (30%), gastrointestinal and genitourinary tracts (10% each), and thorax (5%). Bleeding triggers were spontaneous (20%) and trauma related (80%). Since bleeding in this cohort was non-spontaneous in the majority and was induced by trauma or surgery, all of these events were complicated by anemia requiring packed red cell transfusions. Eight percent of events required no treatment. Reported therapy included cryoprecipitate (33%), fibrinogen concentrate (17%). However, treatment information was unavailable for 42% of events (Table 2b).

Dysfibrinogenemias Eleven subjects (38%) with fibrinogen disorders had dysfibrinogenemia. Diagnostic events were non-surgical bleeding (46%), positive family history (27%), postoperative bleeding (18%), or thromboses (9%). The symptomatic patients (73%) had hemorrhage mainly into skin and mucus membranes (71%), followed by genitourinary (14%), musculoskeletal (7%) and gastrointestinal (8%) tract bleeding. No treatment was administered for 50% of episodes, which comprised of cutaneous bleeding, menorrhagia and postpartum hemorrhage. Cryoprecipitate was used in 38% with no information available in 12%. Cryoprecipitate was used once prophylactically (Table 2b).

Disease-related complications

Homozygous factor deficiencies There were no reported bleeding-related complications for the majority of patients with FVII deficiency and afibrinogenemia; for one-third with FXIII, FX and FV deficiencies; and for one-quarter of individuals with FII deficiency. When noted, mild to moderate anemia was the most common such complication (19–49% of bleeding episodes) for individuals with FII, FVII, FX, FV and FXIII deficiencies; red cell transfusions were required in 10–20% of anemia cases. Musculoskeletal complications, including target joint development and muscle contracture, followed 7–23% of joint and muscle bleeding experienced by those affected with any of the factor deficiencies.

CNS morbidity, including intracranial bleeding and stroke (CVA), complicated 9–22% of events reported with FX, FXIII, FV and FII deficiencies and afibrinogenemia. CVA was reported with FVII deficiency. One FXIII-deficient patient died from intracranial hemorrhage despite FXIII concentrate prophylaxis (Table 3).

Heterozygous factor deficiencies All or most bleeding events (93–100%) associated with FII, FV, FVII and FX deficiency states and dysfibrinogenemia were uncomplicated. However, anemia did complicate 7% and 4%, respectively, of hemorrhage

Table 3 Complications of disease

	Anemia (%)	Musculoskelatal (%)	Central nervous system (%)	Other (%)	None (%)
II					
Homozygous	49	17	11	0	23
Heterozygous	0	0	0	0	100
VII					
Homozygous	19	18	2	0	61
Heterozygous	4	0	1	0	95
X					
Homozygous	34	7	22	0	37
Heterozygous	7	0	0	0	93
V					
Homozygous	36	23	9	0	32
Heterozygous	0	0	0	0	100
XIII	24	15	15	2 ($n = 1$)	44
Fibrinogen					
Homozygous	0	23	22	0	56
Heterozygous	25	8	0	0	67
DysFBN	0	9	1	0	90

Other, Death; DysFBN, dysfibrinogenemia.

associated with heterozygous FX and FVII deficiencies. CVA was reported in 1% of FVII-deficient events and dysfibrinogenemia. Of bleeding associated with fibrinogen abnormalities, 67% was uncomplicated. Nevertheless, mild anemia and musculoskeletal complications were noted following a small number of hemorrhagic events (Table 3).

Treatment-related complications

Patients with FII and heterozygous FV deficiencies as well as hypofibrinogenemia experienced no treatment-related complications. For patients with homozygous deficiencies of FX, FV, FXIII, FVII, afibrinogenemia and dysfibrinogenemia allergic reactions to plasma products were reported with 2–26% of treatment episodes; anaphylaxis occurred in FVII- and FX-deficient patients (2–5%). Venous access device-related complications were observed when patients with severe bleeding manifestations required prophylaxis (homozygous FX, FV, FXIII deficiencies and afibrinogenemia).

All bleeding events responded to initial treatment, except for 2% of bleeds in homozygous FVII deficiency that required an alternative therapeutic modality to achieve hemostasis. Within the entire cohort, only 3% each of patients with FV ($n = 1$) and FXIII ($n = 1$) deficiencies, respectively, developed inhibitors following treatment with FFP and FXIII concentrate.

Transfusion-associated seropositivity was noted for hepatitis A (0.3% of patients); hepatitis B (15.6%); hepatitis C (25%); and human immunodeficiency virus (1%).

Discussion

This is one of the largest reported retrospective studies of rare factor deficiencies. Whereas previous reports focused predominantly on homozygous disorders [12–15], this registry includes comprehensive data on the demographics; circumstances leading to diagnosis, clinical manifestations, treatment strategies and complications associated with both homozygous and heterozygous rare factor deficiencies. As is the case for any registry, the accuracy of information received and, consequently, the validity of the aggregate clinical observations described are somewhat limited by the voluntary retrospective method of data collection by questionnaire. Although we could not ascertain the extent to which the low response rate among HTCs surveyed reflects general population demographics or the absence of such patients at many centers, estimated incidence/prevalence data for these disorders suggest that this database includes only a fraction of American and Canadian individuals with RBDs. It is with these qualifications that we report our data and their interpretation.

When the ethnic distribution of all RBDs patients was compared with that of the general US population, Latinos were significantly over-represented. Based on US demographic data, this observation was not explained by the over-representation of HTCs caring for large Latino populations. Possible skewed genetic predisposition to RBDs in this specific group remains to be explored through systematic gene mutation analysis and population genetics studies.

Previous studies of homozygous patients with RBDs [12–15] did not report an analysis of presenting symptoms or other circumstances leading to diagnosis. In our study, non-surgical bleeding was the most common presenting symptom for individuals with severe RBDs, except for those with severe FVII deficiency, for whom abnormal laboratory screening just as frequently led to diagnosis. However, we and others [13] also observed a high prevalence of postoperative hemorrhage (13–18% of affected individuals) as a presenting manifestation of congenital dysfibrinogenemia, hypofibrinogenemia and severe FX deficiency. As noted previously, a preoperative PT/PTT may not be adequate in detecting occult bleeding disorders or perioperative hemorrhage [16]. We therefore suggest that although not necessarily cost-effective, complete preoperative laboratory screening should include a thrombin time and fibrinogen activity level, as well as a sufficiently sensitive PT and PTT to detect potentially symptomatic low levels of FX.

Following diagnosis, a positive bleeding history was frequently reported for all homozygous factor deficiencies except for FVII. It is unclear whether higher median factor activity levels for FVII ($0.08\ \mathrm{U\,mL^{-1}}$) when compared with the non-fibrinogen disorders (< 0.01–$0.03\ \mathrm{U\,mL^{-1}}$) were partially responsible for this observation in our cohort. When the variable nature of bleeding in our heterozygous FVII deficiency cohort (described below) is also included, our study corroborates data previously published by both Peyvandi and Triplett, which suggest that plasma levels of FVII cannot reliably predict the severity of the hemorrhagic manifestations of this disorder [12,17]. More recently, data by a French group, albeit based on small numbers (three patients), indicate that there could be a gradual decrease in the production of functional FVII protein from the 331Gly→Ser substitution, to 97Gly→Cys mutation and to the 49Gln→Stop nonsense mutation. Hence the suggestion is that a small amount of FVII is sufficient to prevent the occurrence of a severe bleeding phenotype and conventional FVII:C measurement fails to differentiate this gradual decrease in residual FVII activity [18].

The distinct hemorrhagic nature of RBDs, compared with the hemophilias, is suggested by the observation that skin and mucus membranes, not the musculoskeletal system, were the most common site of bleeding among all severe disorders (the site of 63% of all bleeding episodes) [19]. However, life and limb-threatening bleeding was still noted. In the Iranian cohort, FX-deficient patients had the most severe bleeding manifestations [20], whereas our series, which included FXIII deficiency, observed comparably severe bleeding with both FX and FXIII deficiencies. The prevalence of intracranial bleeding in our study was highest for FX deficiency (15%), and lower for FXIII, FII, FV and fibrinogen deficiencies (5–10%). Notably, 53% of the FX- deficient patients had FX activity levels of $< 0.01\ \mathrm{U\,mL^{-1}}$. However, lower median factor activities do not entirely provide a plausible explanation for this observation, as both median FX and FV levels were undetectable. Interestingly, no intracranial hemorrhage was noted in the severe

FVII-deficient cohort in this registry. Intracranial bleeding secondary to homozygous FVII deficiency following birth trauma has been reported with one series [21], and correlates with clinical findings in knock-out FVII animals [22]. However, neither our study nor the previously published reports of Peyvandi *et al*. and Mariani *et al*. corroborate that observation [12,23].

The majority of documented bleeding events associated with afibrinogenemia and homozygous FII, FV, FX, and FXIII deficiencies (>95%) as well as homozygous FVII deficiency (73%) required treatment, attesting to the clinically significant nature of hemorrhage in RBD patients. Only one previous study provided specific information about the treatment or prevention of bleeding, including usage of virally inactivated products and prenatal diagnosis when feasible [12]. EACA and a range of replacement products played important hemostatic roles in surgical prophylaxis. It is interesting that EACA alone controlled a significant amount of bleeding (6–30% of events). EACA has been used to control bleeding in thrombocytopenic patients, and Glanzmann's thrombasthenia [24,25]. Also, in hemophilic patients when dental extractions were carried out along with EACA, less factor replacement was required [26]. This raises questions as to whether for minor mucus membrane bleeding, EACA should be the first product of choice and only in failed cases more specific factor replacement should be considered. Only a collaborative international trial can provide data to justify this line of management. Long-term prophylaxis was only regularly administered for FXIII deficiency (34% of this cohort). Although previously shown to be effective in preventing catastrophic bleeding [27], one failure did occur.

In our study we noted that, particularly in the USA where factor concentrates specifically licensed for the treatment of RBDs are currently unavailable, between 29 and 93% of these severe disorders were treated with blood component therapy which does not undergo viral attenuation. These products also precipitated allergic reactions in up to 26% of recipients. Initial therapy, although variable in nature, proved hemostatic for the majority of bleeding episodes in this group. Nonetheless, hemorrhagic complications did occur. Anemia, mostly mild, was reported in up to half of the homozygous cohort. However, musculoskeletal and CNS sequelae as well as transfusion-associated viral seroconversions were noted in up to a quarter of this group, suggesting that although current treatment practices are effective in the short term, they remain suboptimal in preventing significant morbidity. These data argue for routine vaccination against hepatitis A and B, as well as for regular surveillance of the severe RBD population for the both disease- and treatment-related complications in a comprehensive care setting. These findings also strongly support the value of a rare bleeding disorders registry as both a tool for treatment outcome documentation and a resource for much needed clinical trials of new therapies.

Other treatment-related complications such as inhibitor development, generally uncommon in the RBD population, were noted in our cohort of severe FXIII and FV deficiencies (3% each), and led to the use of bypassing agents to treat hemorrhage. The frequency of inhibitor development in our cohort was similar to previous published data for these disorders [28–30].

Among individuals with heterozygous RBDs, bleeding symptoms led to diagnosis and continued to occur in the majority of FII deficiency and hypo/dysfibrinogenemia patients. However, bleeding uncommonly led to diagnosis, and was only ever reported in half of the FV cohort and a third of individuals with deficiencies of FX. For all disorders, most hemorrhage was still reported to be spontaneous in nature, and not trauma-induced except in the hypofibrinogenemia cohort. In this subpopulation, bleeding in 80% of events was triggered by trauma or surgical challenge leading to severe anemia requiring red cell transfusions.

Plasma factor levels generally predicted the usually mild clinical manifestations affecting predominantly skin and mucous membranes. However, this was not the case for heterozygous FVII deficiency, the largest single group of patients represented in this registry ($n = 88$). On one hand, bleeding frequency in this cohort was among the lowest of any group; only 36% ever demonstrated any bleeding diathesis. Furthermore, as with all other heterozygous disorders, most bleeding was unprovoked and skin/mucous membrane hemorrhage predominated in the symptomatic patient subset. On the other hand, major events such as intracranial hemorrhage (4%) and thromboembolism (1%) were also observed in our study. The paradoxical phenomenon of thrombosis has been previously reported [31], most recently by the steering group for the international FVII registry (G. Mariani, personal communication). As previously described and again noted in this study, plasma FVII levels do not predict disease symptoms [12,15]. Furthermore, although ≥80 FVII gene mutations have so far been identified, genotype–phenotype correlation remains elusive, possibly due to the complex biochemical interactions that both initiate and modulate hemostasis [31,32].

Among all heterozygous disorders, between 20% and 64% of bleeding events required no therapy. When necessary, treatment with blood components and non-specific factor concentrates [(A)PCCs] predominated. Importantly, EACA alone was hemostatically effective for mucous membrane bleeding. Only a minority of patients suffered disease-related morbidity, which most often occurred among fibrinogen disorder patients.

Of the individuals in the registry, 50% had a positive family history (one or more affected member in the family) for their bleeding disorder, despite the primarily autosomal recessive inheritance pattern for RBDs. One possible explanation for this observation is the cohorting of such families in HTCs, where family studies are more likely to be performed to identify heterozygotes. Another less likely explanation, given the heterogeneity of the population studied, may be the prevalence of gene mutations leading to dominant inheritance patterns, as described recently for FVII in an Iraqi Jewish population [33]. Because of the existing low frequency of gene-based diagnosis (5.4%) among our registry subjects, this phenomenon could not be studied further. However, one very important future function of this RBD registry would be to provide a comprehensive

database for the collaborative scientific study of genotype–phenotype correlation. Interestingly, FII and FV knock-out animals and experimental mice rendered FX-deficient exhibit a high degree of embryonic lethality, with early neonatal intra-abdominal and nervous system hemorrhage reported in the latter [34–36]. Yet similarly affected humans not only survive fetal life, but also frequently live out a full life expectancy. Furthermore, they sometimes exhibit minimal or unexpected disease-related symptoms. The disparate outcomes between humans and laboratory disease models have historically been attributed to lack of proven total abrogation of deficient protein in humans. However, the future application of genomics and proteomics could aid in both the prediction of individual phenotype and in the subsequent design of patient-specific treatment approaches.

In summary, the North American Registry of Rare Bleeding Disorders has succeeded in collecting valuable information on these disorders with respect to disease prevalence, genotyping frequency, diagnostic events, clinical manifestations, treatment and prophylaxis strategies, as well as disease and treatment-related complications. Through the cooperation of the Haemophilia Research Society, we plan to expand this registry prospectively in the USA, in the hope of obtaining a more representative sampling of the American population with RBDs. We also intend to continue to develop a common database with other similar national and international registries. In this way, we hope that this and other RBD registries will stimulate future scientist/clinician collaborative study of important genotype–phenotype associations. We also hope that such databases will both spur industry to develop safer and more effective treatment strategies, sorely lacking for these disorders, and facilitate the future clinical trials needed to bring these new products to proper licensure.

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