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ORIGINAL ARTICLE

Coagulation factor activity and clinical bleeding severity in rare bleeding disorders: results from the European Network of Rare Bleeding Disorders

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Summary. *Background:* The European Network of Rare Bleeding Disorders (EN-RBD) was established to bridge the gap between knowledge and practise in the care of patients with RBDs. *Objectives:* To explore the relationship between coagulation factor activity level and bleeding severity in patients with RBDs. *Patients/Methods:* Cross-sectional study using data from 489 patients registered in the EN-RBD. Coagulation factor activity levels were retrieved. Clinical bleeding episodes were classified into four categories according to severity. *Results:* The mean age of patients at data collection was 31 years (range, 7 months to 95 years), with an equal sex distribution. On linear regression analysis, there was a strong association between coagulation factor activity level and clinical bleeding severity for fibrinogen, factor (F) X, FXIII, and combined FV and FVIII deficiencies. A weaker association was present for FV and FVII deficiencies. There was no association between coagulation factor activity level and clinical bleeding severity for FXI. The coagulation factor activity levels that were necessary for patients to remain asymptomatic were: fibrinogen, > 100 mg dL^{-1}; FV, 12 U dL^{-1}; combined FV + VIII, 43 U dL^{-1}; FVII, 25 U dL^{-1}; FX, 56 U dL^{-1}; FXI, 26 U dL^{-1}; FXIII, 31 U dL^{-1}. Moreover, coagulation factor activity levels that corresponded with Grade III bleeding were: undetectable levels for fibrinogen, FV and FXIII, < 15 U dL^{-1} for combined FV + VIII; < 8 U dL^{-1} for FVI; < 10 U dL^{-1} for FX; and < 25 U dL^{-1} for FXI. *Conclusions:* There is a heterogeneous association between coagulation factor activity level and clinical bleeding severity in different RBDs. A strong association is only observed in fibrinogen, FX and FXIII deficiencies.

Keywords: bleeding episode, coagulant activity, phenotype, rare bleeding disorder.

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Introduction

Congenital deficiencies of plasma proteins involved in blood coagulation generally lead to lifelong bleeding disorders. They affect around 65 000 people in Europe and significantly more people in developing countries [1,2]. Rare bleeding disorders (RBDs) represent 3–5% of all inherited coagulation deficiencies, and are usually transmitted as autosomal recessive traits [3,4]. They include inherited deficiencies of fibrinogen, factor (F) II, FV, FVII, FX, FXI, FXIII, and combined FV and FVIII deficiencies (FV + VIII). The global distribution of RBDs is variable, with a prevalence ranging from approximately 1 in 2 million for FII and FXIII deficiencies to 1 in 500 000 for FVII deficiency [3–6]. The prevalence of homozygous or double heterozygous patients in the general population of European descent has generally been low. However, large immigrations from African and Middle East countries with high consanguinity rates have increased the number of patients with RBDs in multiethnic western cities. A new public health concern thus has emerged [6]. A survey conducted by the World Federation of Haemophilia (WFH) showed that at least half of the data currently available on RBDs was obtained from European countries (http://www.wfh.org/2/docs/Publications/Statistics/2008_Global_Survey_Report.pdf).

The WFH started collecting information on RBDs in 2004. The latest survey was reported in 2008, detailing data on the epidemiology of RBDs in 108 countries (http://www.wfh.org/2/docs/Publications/Statistics/2008_Global_Survey_Report.pdf). In addition, several countries have established their own national registries for the collection of data on RBDs [7,8]. However, due to the low prevalence of RBDs, current knowledge on the genetic, laboratory and clinical characteristics of these disorders remains limited [9]. Scientific reports are usually limited to small groups of patients or even single cases. Even the most reliable registries designed to gather detailed information are limited to single aspects of the disease or to the analysis of a single RBD [10–13]. Hence, evidence-based guidelines for the diagnosis and management of this patient population are still lacking.

With these limitations in mind, a European network of treatment centers, entitled the European Network of Rare Bleeding Disorders (EN-RBD), was established and funded by the European Community in the frame of the Public Health Executive Agency (PHEA, now EAHC: Executive Agency for Health and Consumers) and the Directorate-General for Health and Consumers (DG SANCO) in March 2007. The EN-RBD developed and implemented a powerful internet-accessible database (http://www.rbdd.eu) after meticulous standardization of data collection techniques. The EN-RBD is designed to report clinical, laboratory (including phenotypic studies by specific and advanced coagulation tests), genetic and therapeutic information. The network was established in Europe to ensure maximal data entry in the initial stage, and intends to be extended to include more centers from all over the world.

The aim of this first report from the EN-RBD is to explore the relationship between coagulation factor activity level and clinical bleeding severity in patients with RBDs, because clinical experience is that the bleeding risk is not uniformly associated with the level of deficient factor. Results from this study will help identify coagulation factor activity levels that predict protection from bleeding episodes, in order to allocate suitable preventive and management strategies.

Methods

The network

The EN-RBD project, coordinated by the University of Milan, has involved 13 European treatment centers from 11 countries: Belgium (2), Denmark, Germany (2), Greece, France, Ireland, Italy, Serbia, Slovenia, Turkey and the United Kingdom. Some of these centers represented national referral bodies for RBDs. The EN-RBD project was a modification of an existing international database on RBDs called the Rare Bleeding Disorders Database (RBDD). To create the EN-RBD web-application, a web-site technology with an open-source free database engine (MySQL as RDBMS), and an open-source free web server with scripting capabilities (Apache and php) was used. Particular attention was paid to data security and privacy through methods of authentication, authorization and accounting (A-A-A). In compliance with European privacy laws, personal identification data were not entered into the database. The project was approved by the Ethical Review Board of the IRCCS Foundation, Maggiore Hospital, Mangiagalli and Regina Elena, University of Milan, in compliance with all pertinent national and international ethical standards. Written informed consent was obtained from each participating patient.

The correct functioning of the network and of data insertion and reliability was maintained all over the project period during different phases, as described in Table S1.

Data collection

Each participating center had the goal of collecting laboratory phenotype and genotype data, as well as clinical and treatment information, on all patients diagnosed and followed-up at their center through a common data collection model specifically designed for this project.

A total of 592 records on patients with RBDs were cross-sectionally collected and entered into the database over a period of 3 years from April 2007 to April 2010. These included patients who had presented with bleeding episodes or were identified on preoperative screening, as well as their relatives, some of whom had remained asymptomatic until the date of inclusion in the registry. The historical diagnosis of a coagulation deficiency was based on a residual factor plasma activity level below the normal thresholds. For this analysis, retrieved data included demographics (age at data collection and sex), type of coagulation factor deficiency, residual coagulation

factor plasma activity level, and lifelong bleeding histories up to the date of inclusion in the registry, including type of bleeding (hematomas, hemarthrosis, central nervous system bleeding, gastrointestinal bleeding, umbilical cord bleeding, bruising, ecchymosis, minor wounds, oral cavity bleeding, epistaxis and menorrhagia) and the nature of the bleeding symptom (spontaneous or posttraumatic).

Coagulation factor activity level

All factor measurements were done locally using one-stage clotting assay with commercial calibrated pool against international standard in three to eight dilutions. The various methods used to measure coagulation factor plasma activity levels at participating centers are summarized in Table S2.

Clinical bleeding episodes

After consensus between the participating centers, clinical bleeding episodes were classified into four categories of severity relying on the location and potential clinical impact as well as spontaneity of bleeding (Table 1). Patients were classified as belonging to a certain category if they had at least one documented episode matching the defined bleeding severity and no episode matching the higher severity grade.

Statistical analysis

Data are presented as means, ranges or percentages. Linear regression analysis was used to determine the association between coagulation factor activity level (dependent variable) and clinical bleeding severity as a continuous variable (independent variable), with adjustment for age at data collection, sex, and center where diagnosis was made. Coagulation factor activity values corresponding to the lowest detection limit of the specific factor activity assay were assumed to represent complete deficiency of the clotting factor. A sensitivity analysis was also performed using half of the lowest detection limit (i.e. if the lowest detection limit is 5 U dL^{-1} a value of 2.5 U dL^{-1} was used) and results remained essentially unchanged. All *P*-values are two sided with the level of significance set at < 0.05. Analysis was carried out using SPSS v.16 (SPSS Inc, Chicago, IL, USA).

Table 1 Assigned categories of clinical bleeding severity

Clinical bleeding severity	Definition
Asymptomatic	No documented bleeding episodes
Grade I bleeding	Bleeding that occurred after trauma or drug ingestion (antiplatelet or anticoagulant therapy)
Grade II bleeding	*Spontaneous minor bleeding*: bruising, ecchymosis, minor wounds, oral cavity bleeding, epistaxis and menorrhagia
Grade III bleeding	*Spontaneous major bleeding*: hematomas*, hemarthrosis, CNS, GI and umbilical cord bleeding

CNS, central nervous system; GI, gastrointestinal. *Intramuscular requiring hospitalization.

Results

Data on 592 patients with RBDs were retrieved from the network. The mean age of patients at data collection was 31 years (range, 7 months to 95 years), with 11% of patients over age > 60 and 16% under age 10. Patients were equally divided between both sexes (51% women). The numbers of patients with different RBDs included in the EN-RBD are summarized in Table 2. FVII and FXI deficiencies were the most common RBDs, followed by FV, FX, fibrinogen and FXIII deficiencies. FV + FVIII deficiency was rarely observed (so were FII, FXII and other combined deficiencies, which were excluded from further analysis).

Clinical bleeding episodes

After excluding patients with dysfibrinogenemia/dysprothrombinemia ($n = 18$, data not adequately available for separate analyses), data on clinical bleeding episodes were available for 489 patients (93 individuals had a relative in the database and 396 were unrelated to anyone else). A total of 224 (45.8%) patients were asymptomatic. Grade III, II and I bleeding were noted in 61 (12.5%), 117 (23.9%) and 87 (17.8%) patients, respectively. Data on clinical bleeding severity for different RBDs are summarized in Fig. 1. Patients with FXIII, fibrinogen and FX had the highest proportions of patients with Grade III bleeding.

Association between coagulation factor activity level and clinical bleeding severity

On linear regression analysis, there was a strong association between coagulation factor activity level and clinical bleeding severity for fibrinogen, combined FV + VIII, FX and FXIII deficiencies. A weak association with clinical bleeding severity was present for FV and FVII deficiencies, while coagulation

Table 2 Number of patients included in the European Network of Rare Bleeding Disorders database by diagnosis

Type of deficiency	*n* (%)
FVII	224 (38)
FXI	133 (22)
FV	60 (10)
Fibrinogen	46 (8)
FX	45 (8)
FXIII	42 (7)
Combined FV + VIII	20 (3)
FII	6 (1)
FXII	6 (1)
Other combined	10 (2)

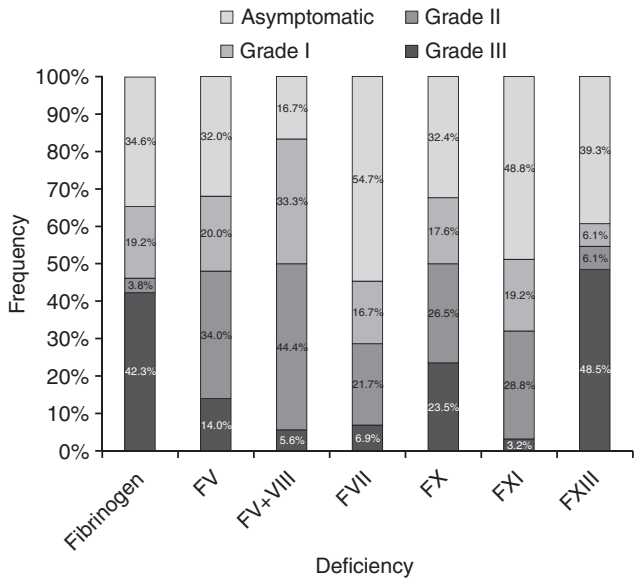

Fig. 1. Distribution of clinical bleeding severity categories within the different rare bleeding disorders.

factor activity level of FXI did not predict clinical bleeding severity (Table 3). The coagulation factor activity levels that were necessary for patients to remain asymptomatic were: fibrinogen, > 100 mg dL^{-1}; FV, 12 U dL^{-1}; combined FV + VIII, 43 U dL^{-1}; FVII, 25 U dL^{-1}; FX, 56 U dL^{-1}; FXI, 26 U dL^{-1}; FXIII, 31 U dL^{-1}. Moreover, coagulation factor activity levels that corresponded with Grade III bleeding were: undetectable levels for fibrinogen, FV and FXIII; < 15 U dL^{-1} for combined FV + VIII; < 8 U dL^{-1} for FVII; < 10 U dL^{-1} for FX; and < 25 U dL^{-1} for FXI.

Discussion

Until now, the only available information on the worldwide prevalence of RBDs could be derived from the RBDD and the WFH global survey (http://www.wfh.org/2/docs/Publications/Statistics/2008_Global_Survey_Report.pdf) [4]. The 2008 WFH survey included data from 108 countries and showed that FVII and FXI deficiencies are the most common RBDs (34% and 32%, respectively), followed by the deficiencies of fibrinogen, FV and FX (7.5%–8%) and FXIII (6%), with the rarest disorders being FII and combined FV + FVIII deficiencies (2–2.5%; http://www.wfh.org/2/docs/Publications/Statistics/2008_Global_Survey_Report.pdf). Our analyses confirm these results.

We have classified RBDs on the basis of clinical bleeding severity using expert opinion, and we report clear associations between coagulation factor activity levels and clinical bleeding severity that differ by the deficient protein. The strongest associations between clinical bleeding severity and coagulation factor activity level were seen in fibrinogen, FX and FXIII deficiencies, where patients with low coagulant activity levels had a higher occurrence of spontaneous major bleeding, while patients with sufficient activity remained asymptomatic. These observations not only confirm clinical experience and findings seen in individual patients [14–16], but also establish a new classification system with practical utility.

FV and FVII deficiencies showed a poor association between coagulant activity level and bleeding severity, whereas FXI deficiency showed no association at all. Platelets can still provide a supply of functional FV in patients with congenital FV deficiency [17–19]. Moreover, FV deficiency has been associated with reduced plasma levels of total and free tissue factor pathway inhibitor antigen, which decreases the FV requirement for minimal thrombin generation in FV-deficient plasma to < 1 U dL^{-1} [20]. These observations may explain the poor association between low coagulation factor activity level and severe bleeding in our study. The heterogeneity in clinical bleeding manifestations and poor predictability of bleeding risk by biological test for FVII deficiency have been observed by others [21]. The lack of association between coagulation factor activity level and bleeding severity in patients with FXI deficiency may be attributed to the role of

Table 3 Linear regression analysis of coagulation factor activity and clinical bleeding severity*

Factor deficiency	Beta (95% CI)	Factor activity for asymptomatic patients (95% CI)	Factor activity for Grade I bleeding (95% CI)	Factor activity for Grade II bleeding (95% CI)	Factor activity for Grade III bleeding (95% CI)
Fibrinogen, mg dL^{-1} (n = 26)	−40.22 (−54.24 to −26.19)	113.40 (22.80–204.01)	73.19 (0–164.14)	32.97 (0–126.39)	0 (0–90.61)
FV, U dL^{-1} (n = 50)	−5.96 (−10.74 to −1.19)	11.94 (0–33.73)	5.98 (0–27.71)	0.01 (0–22.72)	0 (0–18.63)
FV + VIII, U dL^{-1} (n = 18)	−9.52 (−15.07 to −3.96)	43.38 (24.90–61.86)	33.87 (15.71–52.02)	24.35 (4.87–43.82)	14.83 (0–36.98)
FVII, U dL^{-1} (n = 203)	−5.74 (−8.33 to −3.15)	24.87 (14.88–34.86)	19.13 (8.48–29.78)	13.39 (1.54–25.25)	7.66 (0–21.11)
FX, U dL^{-1} (n = 34)	−15.45 (−21.62 to −9.28)	55.91 (28.69–83.12)	40.45 (13.99–66.91)	25.00 (0–52.12)	9.55 (0–38.66)
FXI, U dL^{-1} (n = 125)	−0.35 (−4.02 to 3.32)	26.05 (13.56–38.54)	25.70 (12.97–38.43)	25.35 (11.38–39.32)	25.00 (9.03–40.97)
FXIII, U dL^{-1} (n = 33)	−14.22 (−18.18 to −10.26)	31.07 (10.83–51.31)	16.85 (0–37.13)	2.63 (0–23.71)	0 (0–10.97)

CI, confidence interval. Coagulation factor activity was considered the dependent variable (Y) and clinical bleeding severity was considered the independent variable (X). *Adjusted for age at data collection, sex, and center where diagnosis was made. We also used a regression model taking family dependence into account (93 out of 489 individuals had a relative in the database and 396 were unrelated to anyone else) and this only led to trivial changes in the confidence intervals.

other factors in determining bleeding severity, like the fibrinolytic potential of the site of injury, and activation of the thrombin-activatable fibrinolysis inhibitor [22–24].

Despite a clear correlation between coagulation factor activity level and clinical bleeding severity, the combined FV + FVIII deficiency was mainly associated with minor bleeding, as has been reported in most cases in the literature, which confirms that concomitant presence of these two coagulation defects does not enhance the hemorrhagic tendency observed in each defect separately [25–27].

It should be noted that the antigen level is usually not requested to make the diagnosis and classification of these disorders. However, for fibrinogen and FII deficiencies, evaluation of antigen level discriminates patients with hypo- and dysfibrogenemia or dysprothrombinemia [28–30]. Moreover, higher plasma antigen levels for these two factors may change the clinical picture with combined bleeding and thrombosis observed, especially when other prothrombotic risk factors exist [31,32].

Based on the data reported herein, it appears that the levels necessary to ensure complete absence of bleeding episodes and those that result in major spontaneous bleeding are dissimilar for the different coagulation deficiencies. This is the first report to undertake a formal evaluation of factor activity thresholds associated with bleeding outcomes in RBDs, whereas current practise mainly relies on extrapolations from other bleeding disorders like hemophilia, which can have a totally different disease course. In patients with hemophilia, FVIII and FIX levels of < 1 U dL^{-1} are usually associated with spontaneous and frequent joint bleeding while patients with levels $> 5\%$ remain largely asymptomatic [33]. Nonetheless, other factors may yet influence the observed bleeding pattern, like the time spent with low factor levels [34]. In von Willebrand disease (VWD), patients with VWF levels < 20 U dL^{-1} are most likely to have significant bleeding symptoms. However, family studies show that bleeding and moderately low VWF levels (30–50 U dL^{-1}) do not cosegregate reliably [35]. Our observations carry a significant clinical implication. These thresholds will help distinguish patients who may require a specific treatment only during surgery, from those with a potential for major spontaneous bleeding that requires prophylactic treatment. Levels that ensure patients will remain completely asymptomatic were also identified. This will hopefully be carried forward towards the design of clinical trials, establishment of future management guidelines, or updating current recommendations, which were based on observations from case reports and small case series [9,36]. The coagulant activity level of FXI could not predict clinical bleeding severity, thus a search for alternative indices is called for.

The main limitation of our study is the lack of detailed data on the diagnosis setting (based on presentation with a bleeding episode, positive screening of a relative, or preoperative screening) and the chronology between diagnosis and bleeding episodes. Moreover, the database was, by necessity, based on clinical records, which will predominantly include patients presenting with bleeding symptoms and their relatives. This could have created ascertainment bias with an overestimate of the severity of bleeding. However, this limitation is unlikely to explain differences between the various deficiencies, and the 'threshold' based on the regression analysis, because patients' ascertainment probability may have been dependent on severity of bleeding; it is unlikely to have been dependent on coagulation factor level. Only a population-based screening effort could circumvent this, which, however, is unfeasible given the rarity of the disorders. Future studies clearly discriminating between probands and their relatives, followed over time, will yield more precise estimates. The observed heterogeneity between different RBDs underlines the need for a prospective data gathering tool that allows for adequate assessment of individual RBDs. Undertaking such a task is one of the future aims of the EN-RBD. The variability in the association between the coagulation factor activity level and clinical bleeding manifestations among different RBDs points to the inadequacy of the current available assays to define a minimum residual level of all coagulation factors. For example, in fibrinogen and FXIII deficiencies, current assays are unable to discriminate levels < 5 U dL^{-1} for FXIII and < 10–20 mg dL^{-1} for fibrinogen [14,16]. The role of other global coagulation assays that are able to accurately predict the hemorrhagic risk merits further research.

Our study constitutes the first step in the long road towards establishing evidence-based guidelines for the management of patients with RBDs. The observed association between coagulant activity level and clinical bleeding severity warrants further validation of a bleeding risk-assessment model that takes into consideration other potential modifiers of disease severity.

Addendum

F. Peyvandi designed the study and wrote the manuscript; R. Palla and M. Menegatti designed the database questionnaire, performed quality control, analysed the results and contributed to writing of the manuscript; S. M. Siboni designed the database questionnaire and entered data on patients with RBDs into the database; S. Halimeh, B. Faeser, H. Pergantou, H. Platokouki, P. Giangrande, K. Peerlinck, T. Celkan, N. Ozdemir, C. Bidlingmaier, J. Ingerslev, M. Giansily-Blaizot, J. F. Schved, R. Gilmore, A. Gadisseur, M. Benedik-Dolničar, L. Kitanovski and D. Mikovic were involved in the design of the study, entered data on patients affected by RBDs into the database and critically reviewed the manuscript; K. M. Musallam and F. R. Rosendaal performed statistical analyses and assisted in drafting the manuscript. All authors approved the final version of the manuscript before submission.

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Disclosure of Conflict of Interests

F. Peyvandi receives travel support from NovoNordisk and CSL Behring. P. Giangrande receives speaker's honoraria from NovoNordisk, Bayer Schering, Biotest, Baxter and Octapharma, serves on the advisory board of CSL Behring and receives consultancy fees from Pfizer, NovoNordisk, Biogen Idec, Bayer Schering and Biotest. K. Peerlinck's institution receives research support from Bayer Schering, Baxter, CSL Behring and Pfizer, receives consultancy fees from Pfizer, Bayer Schering and NovoNordisk and receives travel support from Bayer Schering. C. Bidlingmaier receives speaker's honoraria from Baxter, Biotest, CSL Behring, Roche, Pfizer and Bayer Schering, serves on the advisory board of CSL Behring, Pfizer and Bayer Schering, receives travel support from NovoNordisk, and his institution receives research support from CSL Behring and Bayer Schering. J. F. Schved receives research support from LFB, CSL Behring, Novonordisk and Bayer Schering. A. Gadisseur receives speaker's honoraria from CSL Behring and Bayer Schering and his institution receives research support from CSL Behring and Bayer Schering. The remaining authors have no conflicts of interest to disclose.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Data quality assurance scheme.
Table S2. Coagulation factor activity assays utilized by the participating centers.

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