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Establishment of a bleeding score as a diagnostic tool for patients with rare bleeding disorders

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ABSTRACT

Introduction: Bleeding manifestations among patients with rare bleeding disorders (RBDs) vary significantly between disorders and patients, even when affected with the same disorder. In response to the challenge represented by the clinical assessment of the presence and severity of bleeding symptoms, a number of bleeding score systems (BSSs) or bleeding assessment tools (BATs) were developed. The majority of these were specifically developed for patients with more common bleeding disorders than RBDs. Few RBDs patients were evaluated with these tools and without conclusive results.
Methods: A new BSS was developed using data retrieved from a large group of patients with RBDs enrolled in the EN-RBD database and from healthy subjects. These data included previous bleeding symptoms, frequency, spontaneity, extent, localization, and relationship to prophylaxis and acute treatment. The predictive power of this BSS was also compared with the ISTH-BAT and examined for the severity of RBDs based on coagulant factor activity.
Results: This BSS was able to differentiate patients with RBDs from healthy individuals with a bleeding score value of 1.5 having the highest sum of sensitivity (67.1%) and specificity (73.8%) in discriminating patients with RBD from those without. An easy-to-use calculation was also developed to assess the probability of having a RBD. Its comparison with the ISTH-BAT confirmed its utility. Finally, in RBDs patients, there was a significant negative correlation between BS and coagulant factor activity level, which was strongest for fibrinogen and FXIII deficiencies.
Conclusion: The use of this quantitative method may represent a valuable support tool to clinicians.

1. Introduction

Rare bleeding disorders (RBDs) represent 3–5% of all inherited coagulation deficiencies and include fibrinogen, factor (F) II, FV, combined FV and FVIII (FV + VIII), FVII, FX, FXI, and FXIII deficiencies [1].

RBDs are characterized by a wide variety of symptoms ranging from mild to severe, which can vary significantly from one disorder to another and from one patient to another with the same type of disorder. The association between the level of factor in plasma and bleeding tendency can also vary markedly between deficiencies and between patients affected with the same deficiency (e.g. FV, FVII and FXI deficiencies), as recently shown by the European Network of Rare Bleeding Disorders (EN-RBD) study group [2]. Nonetheless, bleeding symptoms are also frequently reported by normal healthy subjects, with at least one episode in up to 25% of the general population [3,4] with the most commonly reported bleeding symptoms being gum bleeding, epistaxis, minor wounds bleeding and menorrhagia in females (average frequency 28, 23, 20 and 35%, respectively).

The clinical appreciation of the presence and severity of hemorrhagic symptoms is an important step in the evaluation of subjects referred for a possible bleeding disorder, including RBDs. However, the evaluation of bleeding symptoms is a challenge because the reporting and interpretation of bleeding symptoms are prone to subjectivity. Significant symptoms may be overlooked because they are considered normal and minimal by affected patients used to have bleeding episodes, or on the contrary, trivial symptoms may be given undue consideration by healthy subjects. Over the years, in response to these challenges, multiple investigators developed a number of bleeding score system (BSSs) or bleeding assessment tools (BATs) in the attempt to standardize

Abbreviations: AUC, area under the curve; BAT, bleeding assessment tool; BS, bleeding score; BSS, bleeding score system; CI, 95% confidence intervals; CNS, central nervous system; EN-RBD, European Network of Rare Bleeding Disorders; F, factor; RBD, rare bleeding disorder; ROC, receiver-operator curve; VWD, von Willebrand disease.

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bleeding histories by identifying questions that best distinguish between patients affected with a bleeding disorder and unaffected individuals [5–10].

Until now, few patients with RBDs were studied using these tools with no conclusive results [11–13]. Two recent reports specifically focused on women with bleeding disorders including RBDs showing that women with RBDs [11] and in particularly with FVII deficiency [12] had a higher prevalence of excessive bleeding at menarche as well as menorrhagia and general bleeding symptoms. Additionally, Siboni et al. [11] showed that in affected women the Sramek bleeding score [6] increased with increasing severity of the coagulation factor defect, although these results are very likely affected by the inclusion of women with von Willebrand disease (VWD) and carriers of hemophilia. Recently, Shapiro and colleagues [13] showed that the bleeding scores, evaluated using the ISTH-BAT [10] did not differ between 35 patients with hereditary dysfibrinogenemia and matched healthy controls. Diagnosis of patients with RBDs has been also performed using the Condensed MCMDM1-VWD Bleeding Questionnaire [9]. Tosetto and colleagues evaluated the diagnostic utility of the Condensed MCMDM-1VWD Bleeding Questionnaire in 215 subjects referred for a possible bleeding disorder [14]. The performance of the BAT varied widely depending on the specific reason for referral and 18 out of 215 enrolled subjects were diagnosed with FXI deficiency [14]. Azzam and colleagues described also the diagnostic utility of the Condensed MCMDM-1VWD Bleeding Questionnaire to predict the presence of a bleeding disorder in 30 women with unexplained menorrhagia [15], showing that a high proportion of women enrolled (20/30 or 66.6%) had an underlying bleeding disorder, but only three patients had a RBD (one each with fibrinogen, FV, and FV + VIII deficiencies) making it impossible to generalize the results to all RBDs.

The described situation emphasizes the need of an ideal scoring system to be applied for the identification of patients with RBDs. Many of the already developed tools were originally designed for more common bleeding disorders, such as VWD, and it is questionable whether they provide the optimal assessment for patients affected with RBDs.

In this manuscript, we provide a novel tool based on a bleeding score (BS) constructed by retrieving data related to previous bleeding types, frequency, spontaneity, extent, localization, and relationship with prophylaxis and treatment of almost 500 patients enrolled in the EN-RBD database, the largest performed study on RBDs so far [2]. The predictive power of our BSS was also compared with the ISTH-BAT [10] in a subgroup of Italian patients and controls. The ability of the BSS to predict the severity of RBDs based on coagulant factor activity was also examined.

2. Patients and methods

2.1. Cases and healthy controls

Throughout the period between April 2007 and April 2010, we identified RBD cases attending 13 European treatment centers from 11 countries: Belgium (2), Denmark, Germany (2), Greece, France, Ireland, Italy, Serbia, Slovenia, Turkey, and the United Kingdom. Data on these patients were collected as part of the EN-RBD project which is described elsewhere [2]. The project was approved by the Ethical Review Board of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Italy, in compliance with all pertinent national and international ethical standards. Written informed consent was obtained from each participating patient.

We included in this study 492 patients with a known bleeding history who were already diagnosed by the participating centers after presenting with bleeding episodes, through preoperative screening, or through family screening. The diagnosis of a coagulation deficiency was based on the measurement of the residual factor plasma activity level below the normal thresholds [2].

We also recruited 107 healthy controls during the same time period. Healthy controls were recruited from among the staff of Milan hospital, their friends or neighbors, they were Italian, unrelated to patients and eligible if in good health and if never referred for hemostasis evaluation.

2.2. The bleeding questionnaire and score system

A questionnaire on bleeding symptoms (Table 1) was administered to each enrolled patient by the referring physician. The bleeding questionnaire was administered to healthy controls by the same doctor who administered the questionnaire to the Italian patients.

For this study, we retrieved data on demographics (age at data collection and sex) and bleeding history up to the date of patient enrollment, including the type (site) of bleeding and its characteristics: frequency, spontaneity, extent, localization, whether it occurred while the patient was on prophylaxis, and type of treatment used to control the bleeding.

For each patient and healthy control subject, retrieved data on bleeding history were categorized according to the type of bleeding and its characteristics, with each item given a score of 1 for presence and 0 for absence as described in Table 1. A score of 1 was given if the subject had experienced the type of bleeding and additionally for each characteristic representing a more severe type of bleeding (frequent, spontaneous, exposure/occurrence while on prophylaxis, extensive, required treatment). When more than one option of treatment was available, higher scores (2 or 3) were given for more aggressive modalities of therapy. Scoring for menorrhagia and for postpartum bleeding was only done for women. Scoring for postpartum bleeding, tooth extraction, tonsillectomy, minor or major surgery was only done for subjects who underwent the procedures. Subjects who underwent these procedures but did not have a bleeding outcome were given the score of −1; in case of prophylaxis administered before the surgery a score of 1 was given, so that the total score for that procedure was 0. These scores were assigned based on consensus agreement between the study investigators, and guided by scoring tools used for other bleeding disorders [17]. For each type of bleeding, an 'index score' was calculated from the sum of scores assigned for all items within its category.

An analysis was conducted to compare our BSS with the ISTH-BAT [10] whose publication coincided with the end of our data collection. The comparison was done on the subgroup of Italian patients/controls whose more specific information requested in the ISTH-BAT questionnaire were easily retrieved from medical records or by interviewing patients/controls. To evaluate whether our BSS can identify the severity rather than only the diagnosis of RBD, we conducted further analysis on patients with RBD to evaluate the correlation and predictive power for our BS against the coagulant factor activity level.

2.3. Statistical analysis

Data are presented as means, ranges or percentages. The BS was extracted from the *Z*-value of a multivariate logistic regression model, in which the outcome RBD versus no RBD was the dependent variable and the symptoms (risk factors) were the independent variables. Covariates entered in the model were age, sex, and the index scores for each type of bleeding. Whether the BS was associated with a diagnosis of RBD was tested by a receiver-operator curve (ROC) analysis. The probability of having a RBD can be calculated from the bleeding score using the formula:

$$\text{Probability of RBD} = 1/1 + e-[BS]$$

To compare the performance of our BSS against the ISTH-BAT, we evaluated the correlation between the two score on Pearson's correlation analysis and compared the areas under the curve (AUC) and their 95% confidence intervals (CI) on a ROC curve analysis for the diagnosis of RBD.