The Diagnostic Approach to Inherited Mild (to Moderate) Bleeding Disorders: A Current Perspective

Rosa Toenges[1,2] Michael Steiner[3]

[1] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, United States
[2] Goethe University Frankfurt, University Hospital, Dept. of Medicine, Hematology and Oncology, Frankfurt am Main, Germany
[3] Medizinisches Labor Rostock, Rostock, Germany

Address for correspondence Rosa Toenges, MD, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, United States (e-mail: rosai_toenges@dfci.harvard.edu).

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We dance round in a ring and suppose, but the secret sits in the middle and knows.

Robert Frost

The Challenge of Defining a Clinical Condition

Minor bleeding events are common symptoms in the primary care setting,[1,2] and the diagnostic approach to inherited mild bleeding disorders (MBDs) should rest on separating pathological bleeding from physiological bleeding corresponding to the extent of injury. However, definitions of MBD in the past were largely based on local practice rather than on internationally agreed criteria. To address this fundamental issue, an International Working Group of the European Hematology Association was formed with the aim to develop a series of guidelines on mild (to moderate) bleeding disorders. In an initial consensus report, fundamentals for a systematic, uniform approach to MBD were formulated.[3] The definition of MBD required to distinguish a bleeding phenotype from "background noise" and to be recognizable and recognized as a disease state. The second unifying criterion was to separate MBD from severe bleeding disorders including severe hemophilia A/B, type 3 von Willebrand disease (vWD), homozygous coagulation factor deficiencies, and biallelic platelet function defects. While appreciating the continuous spectrum of clinical severity in bleeding disorders, grouping of MBD was based more on the clinical bleeding phenotype than on data from laboratory and/or genetic investigations resulting in clinico-pathological criteria. Accordingly, the term MBD should describe any bleeding disorder with a mild to moderate bleeding phenotype. Its distinction from normal may be difficult at the time of initial presentation but may be more overt later in life because of a recurrent mild (to moderate) bleeding phenotype and after a significant hemostatic challenge.

To quantitatively define bleeding phenotypes, the Bleeding Assessment Tool (BAT) recommended by the International Society on Thrombosis and Haemostasis (ISTH) should be used.[4] Fourteen distinctive symptoms with severity assigned according to a scale (from 1 to 4) result in severity-based classification. Symptoms include all bleeding episodes in the past.

Strictly speaking, the consensus report applies exclusively to inherited MBD. However, appreciating that at initial presentation it is largely unknown if the clinical condition under consideration is acquired (as in the majority of cases) or inherited, its general use should be recommended.

Solving a Diagnostic Dilemma

Physical examination forms an indispensable part at initial presentation for suspicious MBD as it may reveal signs and symptoms of former and/or current bleeding episodes. In addition, acquired clinical conditions linked to an increased bleeding risk may be identified, including chronic liver or kidney disease, endocrine disorders, and anemia, to name but a few.

Based on the ISTH BAT score at initial presentation, referred subjects may be categorized into groups with low or high probability of MBD, respectively. Accordingly, standard laboratory coagulation screening applies for the former group, whereas the latter qualifies for an extended laboratory approach. Standard screening includes a complete blood count and peripheral smear, activated partial

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thromboplastin time (aPTT), prothrombin time (PT), fibrinogen, and von Willebrand factor (vWF) analysis. Normal aPTT and PT generally indicate that the plasmatic clotting cascade is intact. However, single or combined mild factor deficiencies may be overlooked and borderline clotting times should be carefully assessed and repeated. Single or combined abnormal aPTT and PT results should be assessed for clotting factor deficiencies and inhibitors, respectively.

The most frequent MBD is vWD type 1. Eleven key recommendations from the recently published guidelines on the diagnosis of vWD should be followed.[5] A diagnosis of vWD type 1 is confirmed at vWF levels <0.50 IU/mL in the presence of abnormal bleeding. Type 1 vWD is considered a prototypic condition where repeat testing may be necessary due to fluctuating vWF levels (e.g., acute phase response) and the affected should be assessed at a baseline state of health.

Thrombocytopenia and/or platelet function defects are important factors to consider in MBD patients with normal plasmatic coagulation parameters. Most platelet function defects are acquired for a variety of reasons including drug treatment, therapeutic procedures, and medical conditions, whereas inherited platelet function defects are rare. The platelet count should be analyzed and stained blood smears from thrombocytopenic samples should be morphologically assessed. Historically, platelet-associated primary hemostasis has been investigated by in vivo bleeding time with various modifications (Duke, Ivy). For the lack of standardization, these methods have been largely abandoned and replaced by an in vitro surrogate. Using citrate-anticoagulated whole blood samples and a cartridge-based analytical system (e.g., PFA-100/200, Siemens), platelet-associated primary hemostasis and vWF function at high shear stress can be quantitatively described. Among several aggregometry-based methods to assess platelet function, light transmission aggregometry as initially described by Born remains the gold standard. Platelet testing can be supplemented by flow cytometry to evaluate glycoprotein expression and granule release. Genetic testing is the ultimate diagnostic tool in inherited platelet disorders.[6]

Putting the Pieces Together

Prevalent MBDs continue to pose a challenge to current medical practice. However, with newer consensus reports and guidelines available, a more structured approach has recently emerged. The value of BAT in establishing the pathological nature of bleeding has been approved. However, they are not helpful in establishing specific diagnoses. A stepwise laboratory testing approach should help diagnosing specific diseases. Unfortunately, a large number of MBD patients remain without a specific diagnosis even after comprehensive and repeated laboratory testing. This condition is referred to as bleeding of unknown cause (BUC). This provisional category is the focus of ongoing research. Incompleteness of laboratory testing in achieving specific diagnoses in MBD is demonstrated by several studies with proportions of BUC ranging from 49 to 75%.[7]

The Way Ahead

Appreciating both, progress and limitations in the current approach to MBD, gaps of knowledge should be identified and solutions be proposed on the way to a more comprehensive understanding of MBD. Targeted genetic analysis should be requested based on coagulation laboratory data to conclusively establish a specific diagnosis (e.g., mild clotting factor deficiency). However, the clinical bleeding phenotype is the net result of innumerable interactions between genetic variations and acquired factors. This highly complex interplay may modify the bleeding phenotype of monogenic MBD. An alternative approach consists of high-throughput sequencing (panel sequencing) including several hemostasis-related genes. A large multicenter study investigating patients with bleeding, thrombotic, and platelet disorders obtained a molecular diagnostic yield of 37.3% by analyzing up to 96 genes.[8] The ISTH SSC (Scientific and Standardization Committee) Subcommittee on Genomics in Thrombosis and Hemostasis has prepared an open-access variant resource (ISTH Gold Variants resource) for the scientific community to submit genetic variants,[9] thus supplementing gene-specific variant databases.

Whereas detailed analysis of primary and secondary hemostasis is commonplace in the diagnostic work-up of MBD, the potential importance of a disturbed fibrinolytic system has been largely overlooked in the past. The topic has recently re-emerged, and one study demonstrated that analysis of the fibrinolytic system (tissue plasminogen activator, plasminogen activator inhibitor, α-2-antiplasmin, euglobulin clot lysis time) has a significant diagnostic yield of 39% in MBD patients.[10]

Routine coagulation tests (aPTT, PT, clotting factor assays) rely on the static endpoint of clot formation. Dynamic global assays (e.g., thrombin generation assays, viscoelastometric tests) may add valuable information covering the overall hemostatic system including less approachable subsystems. Lower thrombin generation potential, lower plasma clot formation, increased clot turbidity, and shortened clot lysis time have recently reported in part of patients previously categorized as BUC.[11]

Conflict of Interest

The authors declare that they have no conflict of interest.

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