

## Preface

# Rare Bleeding Disorders: Genetic, Laboratory, Clinical, and Molecular Aspects

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Welcome to this special issue of *Seminars in Thrombosis & Hemostasis*. Characteristically, each issue of *Seminars in Thrombosis & Hemostasis* is theme driven, with each new issue devoted to a particular theme of relevance to thrombosis and hemostasis. The current issue of *Seminars in Thrombosis & Hemostasis* carries the theme of “Rare Bleeding Disorders” (RBDs) and is an update on a previous issue published in 2009 in this journal.<sup>1</sup> In addition to a comprehensive update on the various rare coagulation factor deficiencies or defects (fibrinogen, FII, FV, FV/FVIII, FXI, and FXIII), the current issue also provides updates on a selected group of rare platelet defects. However, some RBDs have not been updated from the 2009 issue, as we believe there is insufficient new significant information to warrant revision.

The current issue *Seminars in Thrombosis & Hemostasis* represents an attempt to enhance the awareness of various RBDs among treating physicians, clinical and research laboratories, as well as research scientists interested in rare disorders. Each article details, for each RBD, the clinical manifestations, the laboratory assays used in the diagnosis (including problems with the laboratory evaluation), as well as the treatment options. Also, there is considerable discussion on some controversial issues related to these diagnoses, and in some articles, on phenotype–genotypic relationships.

RBDs comprise bleeding disorders that have low prevalence in the general population. The term often refers to inherited deficiencies or defects in coagulation factors including fibrinogen (FI), prothrombin (FII), FV, FVII, combined FV/FVIII defects, FX, FXI, and FXIII. These disorders constitute only approximately 3 to 5% of the coagulation disorders.<sup>2</sup> The clinical conditions associated with these deficiencies can be very diverse, ranging from mild to severe, and the diagnosis can be quite challenging. Much less attention is given to RBDs that alter the function of circulating platelets, some of which are not fully characterized and can also pose diagnostic challenges. Impaired platelet-related hemostatic tests may alert to these diagnoses; however, genetic analysis may

sometimes be required to confirm diagnosis. Platelet defects can be caused by defective platelet receptors that affect the platelet binding to their ligands, impaired platelet structural elements such as dense and  $\alpha$  granules,<sup>3</sup> or altered signal transduction pathways. These disorders include Glanzmann thrombasthenia, Bernard–Soulier syndrome, platelet-type von Willebrand disease (PT-VWD), Gray platelet syndrome, and Scott syndrome.<sup>3,4</sup>

Whether of coagulation factor or platelet origin, the diagnosis and management of patients with RBDs can be difficult. There is little information available about the clinical and laboratory features of some of these diseases and the clinical reports are usually based on single case reports or small case series. In addition, there is a lack of consensus, or lack of awareness regarding expert consensus, with respect to the diagnostic process, which therefore often contributes to mis-/underdiagnosis.

An introduction to this issue by Peyvandi et al provides an overview of the worldwide efforts for classification, diagnosis, and management of RBDs.<sup>5</sup> It updates general information about RBDs published in the 2009 issue,<sup>2</sup> discusses the data collection process worldwide, and also discusses the efforts made by the World Federation of Hemophilia (WFH; <http://www.wfh.org>) and the International Rare Bleeding Disorders Database (RBDD; [www.rbdd.org](http://www.rbdd.org)) in assessing the worldwide prevalence of RBDs. This has more recently been added to by the European Network of the Rare Bleeding Disorders and the Rare Bleeding Disorders Working Group under the umbrella of the FVIII and FIX Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis. This article also discusses efforts to establish a consensus regarding the classification based on clinical severity, issues related to the laboratory diagnosis and consensus (as related to the factor level in making the diagnosis), and also the minimum coagulant activity required to prevent bleeding. The article concludes that prospective large data collection in a multicenter multinational study is required to fill the

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gaps in our knowledge of RBDs and to enable us to move toward future clinical trials.<sup>5</sup>

The second article by de Moerloose et al discusses various forms of fibrinogen defects.<sup>6</sup> It details the clinical and laboratory diagnosis of patients with afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia. It also provides new information regarding the genetics of this disease. Since the first report of a genetic mutation in 1999, and even since the last issue on this topic in this journal few years ago,<sup>7</sup> large numbers of mutations have been described. Despite the increase in the magnitude of genetic analysis in this field, there is no clear relationship between the molecular defect and the risk of thrombosis, and the explanation for the observed variability of clinical manifestations is still lacking and the genotype–phenotype correlations difficult to establish. Many challenges remain, particularly to achieve more appropriate prevention and treatment of these diseases.<sup>6</sup>

The third article is by Lancellotti et al,<sup>8</sup> and it provides an update on the previous review on FII deficiency published in 2009 in *Seminars in Thrombosis & Hemostasis*.<sup>9</sup> This update focuses on the molecular diagnosis of FII deficiency caused by close to 40 different mutations and manifesting in two phenotypes, the true hypoprothrombinemia (type I; quantitative deficiency) and (2) dysprothrombinemia (type II; qualitative deficiency), and sometimes in both when coexisting in the compound heterozygous state. Prothrombin, the source of thrombin, is essential for the development of mammalian organisms and an undetectable plasma prothrombin is incompatible with life. In addition to its procoagulant and anticoagulant effects, thrombin affects the activity of multiple cells that are engaged in several processes of the vascular and immune system such as platelets, endothelial cells, vascular smooth muscle cells, monocytes, T-lymphocytes, fibroblasts, and mast cells. In addition to clinical, laboratory diagnosis, treatment via prothrombin products including recent developments in therapy, the genetics and structure and function relationships were also discussed.<sup>8</sup>

The fourth article by Thalji and Camire<sup>10</sup> discusses the deficiency of FV and its profound impact on thrombin generation, and it represents another update to a review previously published in this journal.<sup>11</sup> Deficiency of FV due to inherited or acquired conditions results in a broad spectrum of bleeding symptoms. The disease is clinically heterogeneous; therefore, predicting an individual patient's clinical phenotype can be difficult as many patients with extremely low levels of FV do not bleed or only experience minor bleeding. Furthermore, some patients with undetectable levels of FV experience relatively mild bleeding. In addition to the clinical manifestations, diagnosis, and treatment detailed in this article, the recent advances highlighting the importance of platelet FV and other modifiers that influence bleeding tendencies and FV's ability to promote thrombin generation are discussed.<sup>10</sup>

The fifth article is by Zheng and Zhang<sup>12</sup> who provide an update on the combined deficiency of FV and FVIII (F5F8D)—an RBD characterized by simultaneous reduction of both coagulation factors. The article summarizes recent reports on the clinical presentations, treatments, and molecular mechanism of F5F8D. Genetic studies have highlighted two

genes being responsible for an intracellular trafficking (endoplasmic reticulum-to-Golgi transport) pathway required for the efficient secretion of FV and FVIII. These are the (lectin mannose-binding 1 (*LMAN1*) or multiple coagulation factor deficiency gene 2 (*MCFD2*) genes. The article focuses on the molecular mechanism of F5F8D that facilitated an understanding of the unique roles of *LMAN1* and *MCFD2* genes in the secretion of FV/FVIII and highlighted the clinical benefits of the improved treatments of this bleeding disorder.<sup>12</sup> Combined FV and FVIII deficiency was also featured in the earlier issue on RBDs.<sup>13</sup>

The sixth article is by Duga and Ophira<sup>14</sup> who provide a rich discussion of FXI deficiency—an injury-related bleeding disorder, common in Ashkenazi Jews but rare worldwide—and an update to a previous review on the same topic.<sup>15</sup> There are more than 220 mutations in the FXI gene reported in patients with FXI deficiency, 7 of which show a founder effect. In addition to a detailed review of the phenotypic and genotypic analysis and the molecular basis of this bleeding disorder, the article discusses special issues in women and highlights the value of studies in animal models with FXI deficiency. Treatment of patients with severe FXI deficiency remains challenging because factors influencing bleeding risks are still unknown and patients with severe deficiency paradoxically develop thrombosis. Problems with laboratory diagnosis and the value of global hemostatic assays are highlighted. Treatment strategies and problems with treatment are also addressed.<sup>14</sup>

The final coagulation factor defect discussed in this issue is by Schroeder and Kohler and on factor FXIII deficiency,<sup>16</sup> and the article provides an update on the previously published review on the same topic in the 2009 issue.<sup>17</sup> The diagnosis of this disease is challenging at both a clinical and laboratory level. The laboratory challenge compared with other RBDs is related to difficulties associated with timing of blood sampling, assay types, and interpretation of results. The article highlights the importance of newer specific FXIII assays and their principles to avoid any missed diagnosis of FXIII deficiency and details the epidemiology and molecular genetics. An update on the therapeutic options for patients is also provided.

In this issue of *Seminars in Thrombosis & Hemostasis*, we also wish to provide the reader with an opportunity to explore other RBDs caused by platelet defects. We begin with a rich overview by Nurden et al on Glanzmann thrombasthenia (GT),<sup>18</sup> the principal inherited disease of platelets and the most commonly encountered disorder of an integrin. The disease is caused by quantitative or qualitative deficiencies of platelet integrin  $\alpha_{IIb}\beta_3$  and is characterized by spontaneous mucocutaneous bleeding and an exaggerated response to trauma due to platelets that fail to aggregate when stimulated by physiologic agonists. The disease results from a defect of two genes—*ITGA2B* and *ITGB3*—and the clinical heterogeneity remains poorly understood. The article provides a panorama of genetic mutations that explains the bleeding tendency and further examines deep vein thrombosis as an unexpected complication of GT. Finally, new approaches for treatment are highlighted.<sup>18</sup>

Next in line is another rich overview by Andrews and Berndt of a common platelet defect characterized by low

platelet count and abnormally large platelets, namely Bernard–Soulier syndrome (BSS).<sup>19</sup> The defect here lies in the surface expression of glycoprotein (GP)Ib-IX-V, a platelet-specific adhesion-signaling complex, and resulting from mutations in its major ligand-binding subunit, GPIb $\alpha$ . The article discusses history, subtypes, and diagnosis and further reflects on how studies of BSS have contributed to platelet biology and facilitated the understanding of the role of GPIb $\alpha$  beyond hemostasis.<sup>19</sup>

The next article in the issue is by Othman et al<sup>20</sup> who provide an extension to the role of platelet GPIb $\alpha$  in hemostasis and present an update to, and new information on, PT-VWD compared with previous chapters in earlier STH issues.<sup>21,22</sup> PT-VWD is an underdiagnosed, underreported/misdiagnosed, and understudied disorder despite ongoing worldwide efforts. PT-VWD is a platelet function defect that is often ignored and mistakenly grouped unintentionally with VWD defects. This autosomal dominant bleeding disorder is unique among platelet disorders because it is characterized by platelet hyperresponsiveness rather than decreased function due to gain of function mutations in the platelet *GPIBA* gene, which codes for the platelet VWF receptor, GPIb $\alpha$ . This article provides not previously reported information with respect to understanding of the theory and mechanisms of different PT-VWD mutations (including the deletion mutant, located outside the VWF binding site) by surveying all the available GPIb $\alpha$  crystal structures and provides a framework of a new hypothesis for the molecular basis of the disease. The molecular behavior of the hyperresponsive platelet GPIb $\alpha$  in hemostasis and beyond remains poorly understood. With the documented role of platelets beyond hemostasis together with the wide array of ligands for GPIb $\alpha$ , the door is open to investigate the influence of various PT-VWD mutations on other physiological/pathophysiological processes such as inflammation and atherosclerosis. The article also details worldwide efforts to improve diagnosis of PT-VWD and highlights the need for an international systematic study to further our understanding of the phenotype and the influence of the hyperresponsive GPIb $\alpha$  beyond haemostasis.<sup>20</sup>

Next is an article by Kubisz et al<sup>23</sup> about a rather thrombotic (and not a bleeding) disorder—a form of thrombophilic thrombocytopeny with a familial occurrence and autosomal dominant trait manifesting in young adults and associated with fertility problems in women. The disease, known as sticky platelet syndrome (SPS), is characterized by an in vitro platelet aggregation in response to low concentrations of adenosine diphosphate and/or nephrine and results in the clinical phenotype. This syndrome is associated with both venous and arterial thrombosis and causes pregnancy-related complications but the incidence in general population is yet to be determined. Despite efforts in investigating several platelet glycoproteins as potential causes for the inherent platelets' activation and aggregation defect, the precise defect responsible for the syndrome and the exact pathogenesis of SPS remains insufficiently explained. Most of the information provided in this article is based on the authors' own patient cohort.<sup>23</sup>

We complete this issue by discussing the paradox of thrombosis in RBDs by Ruiz-Saez.<sup>24</sup> Thrombosis has previously been reported in patients with bleeding disorders such as hemophilia and VWD.<sup>25</sup> Some RBDs, despite being recognized for their severe bleeding tendency, can similarly be associated with thrombotic events. Among the RBDs, those most commonly associated with venous or arterial thrombosis are afibrinogenemia, FVII, and FXI deficiencies. The pathogenesis of thrombosis in bleeding disorders is multifactorial and often related (as discussed in this article) to coexistence of inherited or acquired thrombotic risk factors linked to certain specific characteristics of the underlying defect. The article also highlights treatment strategies and underscores the value of controlling the known cardiovascular disease risk factors in these patients, while indicating that treatment of thrombosis in RBDs in general remains an obvious challenge.<sup>24</sup>

Finally, we need to recognize that studying rare diseases in general as well as RBDs in particular requires that we maximize resources and coordinate/combine worldwide efforts. This will enable us to improve the understanding of the pathophysiology, promote diagnostic tools, reach consensus, and enhance patients' care. There are several key elements to this process: (1) worldwide sharing of information, data, and samples; (2) exchanging expertise among clinicians and scientists; (3) supporting publications of single case reports or small case series on these rare diseases (It is to be noted that there are several journals that are specialized to rare disease such as *Orphanet Journal of Rare Diseases*, <http://www.ajrd.com/>, and *Rare Diseases* journal, <http://www.landesbioscience.com/journals/rarediseases/>); (4) providing worldwide avenues for collaboration such as The International Rare Diseases Research Consortium (IRDiRC; [http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc\\_en.html](http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc_en.html)); (5) building effective research grants/collaborations on common research projects (A good example here is the "European Research Projects on Rare Diseases" Joint Transnational Call <http://www.e-rare.eu/joint-call/5th-joint-call-european-research-projects-rare-diseases-jtc-2013> launched by the ERA-NET <http://www.e-rare.eu/>); and (6) generating international working groups to enhance molecular understanding of rare disease (The ThromboGenomics Working Group of the ISTH Scientific and Standardization Committee <https://haemgen.haem.cam.ac.uk/thrombogenomics> is a good example and is currently focusing on developing a sequencing approach to help streamline the diagnosis of patients with known rare bleeding and platelet disorder.).

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