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Inherited platelet functional disorders: General principles and practical aspects of management

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ABSTRACT

Platelets are a critical component for effecting hemostasis and wound healing. Disorders affecting any platelet pathway mediating adhesion, activation, aggregation and procoagulant surface exposure can result in a bleeding diathesis. Specific diagnosis even with advanced techniques which are unavailable to most centers is often difficult. Inherited platelet function disorders therefore represent a heterogeneous and complex collection of disorders with a spectrum of bleeding severity, from relatively mild (and easily missed or misdiagnosed) to severe bleeding phenotype with salient diagnostic features. We advocate the use of bleeding assessment tools to help identification of patients and more importantly for assessment of individual patient bleeding phenotype to guide management decisions for treating and preventing bleeding. The complex management of these patients is best coordinated in a multidisciplinary comprehensive care clinic setting expert in managing bleeding disorders and associated complications, with particular attention to the physical and psychosocial health of patients and their families. Depending on the bleeding phenotype, the location and severity of bleeding, and the nature of an invasive procedure, available treatment modalities range from conservative measures using local pressure, topical thrombin, fibrin sealant, antifibrinolytics etc. to the use of systemic haemostatics such as desmopressin (DDAVP), platelets and recombinant human activated factor VII (rFVIIa). This review will provide opinions on the practical aspects and general management of inherited platelet function disorders, with discussion on the mechanism of action, and the pros and cons of various hemostatic agents. Finally, the prospect of curative treatment for patients with severe bleeding phenotype refractory to available treatments and with poor quality of life will be briefly discussed.

1. Introduction

The physiologic function of platelets is to participate in the initial phase of hemostasis to prevent excessive bleeding when there is a vascular injury [1]. Platelets in the circulation normally do not interact with intact endothelium. At the site of vascular injury, platelets become adherent to the subendothelium via the interaction of platelet surface receptors with von Willebrand factor (VWF) and the exposed collagen. Receptor binding signals platelet activation causing shape change, exposure of negatively-charged membrane phospholipids and release of storage granule contents, some of which further activates and recruits adjacent circulating platelets. Interaction of activated platelet receptors with VWF and fibrinogen form platelet aggregates (platelet plug) that cover the wound site allowing for primary hemostasis. Simultaneously, tissue factor becomes expressed at the wound site to begin activation of the clotting cascades. Activated platelets provide a negatively-charged phospholipid surface to support efficient interaction of the clotting factors for thrombin generation. This creates the crosslinked fibrin network which reinforces the platelet plug for stable clot formation and secures final (secondary) hemostasis. Inherited platelet function disorders (IPFDs) therefore can be classified [2–5] according to defects of:

- adhesion (VWF receptor GP1b/IX/V, collagen receptors GPVI, α2β1);
- activation (via G protein-coupled receptors, e.g., the ADP receptors, P2Y1, P2Y12);
- signal transduction pathways and secretion (alpha granules, dense granules);
- aggregation for platelet thrombus formation (fibrinogen and WVF receptor αIIbβ3); and

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- Presentation of the negatively-charged phospholipid procoagulant surface for coagulation factor interaction on activated platelets.

A brief description can also be found in the chapter by Rand, Reddy and Israels in this Journal issue [6].

Quantitative or qualitative platelet defects therefore result in a bleeding diathesis with mucocutaneous bleeding as the common clinical manifestation. Mucocutaneous bleeding can include epistaxis, gum bleeding, heavy menstrual/uterine bleeding, gastrointestinal and genital urinary bleeding as well as peripartum/postpartum bleeding. The IPFD bleeding disorders are generally mild but can be severe in some disorders such as Glanzmann's Thrombasthenia (GT, defect of platelet surface integrin αIIbβ3 receptor for fibrinogen and VWF in platelet aggregation) and Bernard-Soulier syndrome (BSS, defect of platelet surface glycoprotein Ib-IX-V receptor for von Willebrand factor in platelet adhesion). Excessive bleeding following trauma or surgical procedures is a concern in any of the platelet function disorders.

In this chapter, we will describe the general principles for the management of bleeding in IPFD, following a description on the general clinical identification of these patients.

2. Patient identifcation

Diagnosing inherited platelet function disorders is often fraught with difficulty. In a worldwide survey of 202 laboratories in 37 countries, the only common criterion to define patients with suspected IPFD was mucocutaneous bleeding and no acquired cause, which is rather non-specific [7]. The same survey study reported ~14,000 patients were investigated yearly and 60% had no identified defect. Of the remaining 40%, only 8.7% had a confirmed molecular defect. More severe IPFDs such as GT and BSS have clinically evident bleeding and well-characterized, highly specific diagnostic tests making the diagnosis relatively straightforward. However, the more heterogeneous mild IPFDs lack consensus in diagnostic algorithm due to the complexity of platelet activation pathways and the lack of availability of precise laboratory testing. More advanced molecular testing like next generation sequencing (NGS) [8], which is not available in most laboratories, may be helpful in identifying a causative defect. Furthermore, many patients with milder bleeding phenotype often do not come to attention for diagnostic workup. Thus, the reported prevalence of IPFDs is most certainly underestimated. Regardless, clinical evaluation with attention to bleeding phenotype, family history and inheritance pattern of bleeding diathesis, and clinical manifestations of syndromic IPFDs is key to making the correct diagnosis.

2.1. Clinical assessment and bleeding assessment tools

Work up for a bleeding disorder generally begins when a patient presents with bleeding symptoms although some patients may be investigated because of a family history of a bleeding diathesis. Iron deficiency anemia may also prompt assessment of mild bleeding disorders or IPFDs since chronic epistaxis, frequent gum bleeding, heavy menstrual bleeding and gastrointestinal bleeding are common contributors to blood loss in these patients. Patient personal and family bleeding history is therefore the first clinical step towards accurate diagnosis. However, determining whether bleeding is really abnormal is one of the more difficult parts of the evaluation.

Bleeding history tends to be subjective and there is considerable overlap with bleeding symptoms experienced by the normal population. The use of bleeding assessment tools (BAT) is helpful to make this aspect of the bleeding history more systematic, objective and quantitative. Use of BATs allow us to objectively determine the severity of the patient's bleeding phenotype which is important for developing a management plan for the treatment of bleeding and surgical prophylaxis.

Validated assessment tools include the ISTH (International Society for Thrombosis and Haemostasis) BAT for both adults and children [9], the Condensed MCMDM-1 VWD for adults [10] and the Pediatric Bleeding Questionnaire for children [11]. The Condensed MCMDM-1 VWD has been validated for the diagnosis of von Willebrand disease (VWD) but many investigators use this as a screening tool for other bleeding disorders with heterogeneous bleeding presentations. The BAT questionnaires and scoring guides can be downloaded from the World Federation of Hemophilia (WFH) website (http://elearning.wfh.org/resource/compendium-of-assessment-tools/) [last accessed May 14, 2018].

For more severe IPFDs, bleeding symptoms often manifest in childhood and particular attention should be given to cephalohematomas, circumcision bleeding, and umbilical stump bleeding. Intracranial bleeding and allo-immune thrombocytopenia can occur in neonates born to women with anti-platelet antibodies in disorders such as GT or BSS. The ISTH BAT [9] and Pediatric Bleeding Questionnaire [11] incorporates questions about these bleeding symptoms which can be missed on history without the objective guidance of a BAT. It is recognized, however, that none of the BATs are validated to predict IPFD as has recently been demonstrated in a study using ISTH BAT [12].

2.2. Medication history

A detailed medication history including 'over-the-counter' drugs (e.g. nonsteroidal anti-inflammatory drugs, NSAIDs) and herbal remedies, is crucial when evaluating for bleeding disorders as they are common causes for acquired coagulation or platelet functional defects.

2.3. Family history

Family history is essential in evaluating for IPFDs for a couple of reasons. Firstly, thrombocytopenia, either isolated or associated with other cytopenias, can be seen in IPFDs with inherited thrombocytopenia, especially in children, although some manifest later in adult life. IPFDs can be misdiagnosed as an immune thrombocytopenic purpura (ITP) if attention is not given to family history of thrombocytopenia. Clinicians should also re-evaluate patients labeled as ITP who have a poor response to the standard treatment (e.g. steroids, IVIG). Familial thrombocytopenias and/or failure to respond to ITP treatment should trigger investigations for IPFDs including blood smear to assess platelet morphology and white blood cell inclusions. Secondly, although certain IPFDs such as GT, Hermansky-Pudlak syndrome (HPS), are rare (~1:1 million), variability in prevalence is seen in certain ethnicities and regions with high rates of consanguinity, so that the possibility of consanguinity should be part of the family history inquiry. GT has a prevalence of 1:200,000 or higher in certain areas of Newfoundland and Labrador and in other remote regions in Canada, Iran, Jordon, Saudi Arabia, Iraqi Jews and in French Gypsies where consanguineous marriages are more common; while HPS is highly prevalent in parts of Puerto Rico where 1:1800 people are affected [13].

2.4. Physical evaluation

Physical findings should include not only bleeding manifestations but also evidence of renal and hepatic disease that can cause acquired platelet dysfunction or coagulation factor deficiencies. Clinical assessment should also include personal and familial syndromic manifestations associated with some of the IPFDs such as renal, ocular, otologic (e.g. neurosensory hearing loss), pulmonary (e.g. pulmonary fibrosis), cardiac (e.g. velocardiofacial syndrome) cutaneous (e.g. albinism, skin hyper-elasticity, eczema), immunologic (e.g. frequent infection) and skeletal abnormalities as well as familial occurrence of leukemia and myelodysplasia [2].