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Bleeding disorders - Section 3

Rare bleeding disorders - Diagnosis and treatment

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Take-home messages

- Among rare bleeding disorders apart from congenital hemophilia, observational findings from international registries provide the only feasible large-scale data source.
- Laboratory assessment and especially molecular techniques enable accurate diagnosis.
- Recommendations for hemostasis control include mainly replacement of the missing coagulation factors (unless presence of inhibitors renders it impossible).
- Future gene therapy is promising and novel disruptive alternatives may be interesting for treatment and prophylaxis of patients with RBD as well, following clinical trials.

Introduction

Rare diseases are defined as life-threatening or chronically debilitating conditions that have a prevalence of fewer than 1:2000 according to the European Union or 1:1250 according to the USA federal Hemophilia Treatment Center Network.[1] Rare bleeding disorders (RBDs) are reported in most populations, with incidences varying from 1:5000 for hemophilia A (HA), to 1:30,000 for hemophilia B (HB), to the much rarer 1:500,000 for FVII deficiency, and 1-3:1,000,000 for prothrombin or FXIII deficiency).[1,2]

The European network RBD project confirmed that FVII and FXI deficiencies comprise most (39%-29%) of the RBDs, whereas fibrinogen (8-9%), FXIII (6%), FV+FVIII (3%) and prothrombin (1%) disorders are rarer. Most RBDs are inherited as autosomal recessive, however, heterozygous carriers may confer an unpredictable propensity for bleeding.[3]

Current state of the art

Severe RBDs often present with acute bleeding symptoms that may occur either spontaneously or following a minimal trigger. In neonates, these include cephalhematomas, skin bleedings and injury-related bleeding following invasive procedures (e.g., circumcision) or sites of peripheral venipunctures. Persistent oozing from the umbilical stump is typical of defective fibrinogen or FXIII deficiency. Hemarthroses, which are typical for severe hemophilias, rarely occur before ambulation. A small proportion of infants with RBDs present with intracranial hemorrhage (ICH), as frequently reported in FVII, FX and FXIII deficiencies (prevalence up to 25%) and rarely in afibrinogenemia, FII, FV and vitamin K-dependent coagulation factor deficiencies.[2,4]

In contrast, some patients with contact pathway deficiencies, e.g., FXI deficiency, may present only after adulthood with post-trauma or surgical bleeding typical for tissues in which there is high fibrinolytic activity (e.g., teeth extractions, urinary and prostate surgeries).[1,3]

Combined FV+FVIII deficiency is associated with a mild bleeding phenotype, whereas combined vitamin K deficiency resulting from inherited defects in activation (γ-carboxylation) of the vitamin K-dependent factors (FII, FVII, FIX, and FX) presents early with serious bleeding events, including ICH.[2,5]

Women with RBDs may present with menorrhagia, bleeding ovarian cysts or corpus luteum, post-partum hemorrhage or other obstetric complications, including recurrent miscarriages due to the roles that deficient factors (e.g., FXIII) play in placental implantation and pregnancy maintenance.[1,3,5]

Critical and unique bleeding manifestations of various RBD are summarized in Table 1.

When acute severe new bleeding symptoms appear unexpectedly at older ages, acquired coagulation inhibitors should be ruled out.

Laboratory diagnosis

The diagnosis of RBD is usually straightforward, requiring standard coagulation tests preceded by special assays for relevant factors activity. Antigenic assays are essential for diagnosis, classification and treatment, especially for patients with

dysfibrinogenemia and dysprothrombinemia, both associated with an increased thrombotic risk.[1] Normal prothrombin time (PT) and partial thromboplastin time (aPTT) screening test results do not exclude defective FXIII or thrombocytopathy. Notably, patients may also present with bleeding symptoms and a prolonged PTT due to the presence of autoantibodies against FVIII. In these rare cases, aPTT does not correct after mixing with normal plasma. When a patient's plasma is incubated with FVIII, its residual activity defines the FVIII inhibitor level, as measured by Bethesda units.

Thrombin generation (TG) and rotating thromboelastogram (ROTEM) are complementary global clotting tests, which may be used as indicators of overall hemostasis. TG was studied in RBDs as a predictor for bleeding risk and as a tool for monitoring patients. Notably, test standardization is still required before it will be applicable for widespread clinical use. ROTEM, which evaluates clot kinetics and fibrinolysis in whole blood, enables the assessment of fibrinogen, FXIII deficiency and platelet disorders that are sometimes misdiagnosed by other assays.[6-8] In an era in which genetic knowledge is growing, identification of the causative mutation of RBDs is becoming the definitive diagnostic method.[9] In an attempt to prevent future morbidities, proper molecular diagnosis enables prenatal familial counseling by the use of pre-genetic determination together with in vitro fertilization to select healthy embryos prior to implantation.[10]

Table 1. Special characteristics of rare bleeding disorders.

	Known gene defect	Potential gene therapy	Unique serious manifestation	Replacement therapy	Non-replacement therapy and future options
Fibrinogen deficiency	FGA, FGB, FGG(4q28)	N/A	Thrombosis Bleeding from umbilical stump	Pd Fibrinogen concentrate/FFP/Cryo	
Prothrombin deficiency	F2(11p11-q12)	N/A	Mucosal bleeding Hemarthrosis ICH	PCC/ FFP	
FV deficiency	FV (1q24.2)	N/A	Epistaxis umbilical stump bleeding Muscle hematoma Hemarthrosis	FFP/FV (clinical study)	Platelet transfusion
FVII deficiency	FVI(I 13q34)	Yes* *No human trials	ICH hemarthrosis	rFVIIa /PCC/FFP/ PdFVII	
FVIII deficiency (hemophilia A)	FVIII(Xq28)	Yes	ICH Bleeding at circumcision Hemarthrosis	PdFVIII/rFVIII/ EHL FVIII	Concizumab (anti-TFPI)/Fitusiran(siRNA) /emicizumab
FIX deficiency (hemophilia B)	FIX(X- long arm)	Yes	ICH Bleeding at circumcision	PdFIX/rFIX/EHL FIX	Concizumab (anti-TFPI)/Fitusiran(siRNA) Hemarthrosis
Hemophilic patients with inhibitors		No	ICH Bleeding at circumcision Hemarthrosis	FAIBA/rFVIIa	Concizumab (anti-TFPI) /Fitusiran(siRNA) /emicizumab HA.
Combined FV and FVIII deficiency	LMAN1(18q21.3-q22) MCFD2 (2p21-p16.3)	N/A	Bleeding at circumcision Post-surgery/ trauma bleeding	FFP- rFVIII	DDAVP
FX deficiency	FX(13q34)	N/A	GI bleed ICH Umbilical stump bleeding	PCC/PdFX	
FXI deficiency	FXI(4q35.2)	N/A	Cases of MI and DVT have been reported	PdFXI	
FXIII deficiency	FXIII(6p24-p25) FXIIIB(1q31-q32.1)	N/A	Delayed wound healing Miscarriages ICH	rFXIII A subunit/ PdFXIII /FFP/cryo	
Vitamin K-dependent coagulation factors deficiency	GGCX(2p12) VKORC1(16p11.2)	N/A	Skeletal abnormalities ICH Umbilical stump bleeding	Vitamin K/PCC/FFP	

R- recombinant; PCC- prothrombin complex concentrate; FFP- Fresh-frozen plasma; Pd- plasma-derived; cryo- cryoprecipitate; ICH- intracranial hemorrhage; HA- hemophilia A; HB- hemophilia B; GI- gastrointestinal; DVT- deep vein thrombosis; MI- myocardial infarct.

Treatment

Current management of RBDs is mainly based on replacement therapy. In countries with abundant resources, the majority of RBDs are treated by specific factor concentrates, mostly plasma-derived, although recombinant products are also available[11] (Table 1). Adjuvant therapies, such as antifibrinolytics, used alone or in combination with replacement, as well as estrogen/progestin preparations can be considered for milder mucosal hemorrhages or heavy menstrual bleeding.

In some RBDs, such as FXI deficiency, treatment may be required only directly following trauma or during surgical procedures. On the other hand, standard of care of other RBDs, such as HA, HB, FXIII and severe FVII deficiency, is regular prophylactic therapy. Extended half-life coagulation products that were recently developed for hemophilia may improve hemostatic efficacy and patients' adherence to therapy.[12] Formation of antibodies directed against the missing factor concentrate is a complication that may render factor replacement therapy ineffective.[13] Acquired hemophilia A (AHA) is a severe bleeding disorder caused by autoantibodies against clotting FVIII. With an estimated annual incidence of 1.3 to 1.5 per million, AHA is also a rare (although not a congenital) bleeding disease.[14] Treatment may involve the use of bypass agents to control hemostasis, while immunomodulation (with an increasing role for rituximab) may be required to eradicate the inhibiting antibodies.

Most congenital RBDs are monogenic diseases, and even a small increase in factor activity levels can profoundly improve the disease phenotype. This makes RBDs ideal candidates for gene therapy. The greatest progress has been achieved in hemophilia B,[15] whereas the more challenging therapy for HA is currently being tested in clinical trials.[16,17]

Other new treatments are represented by non-replacement therapies. Emicizumab, a bispecific antibody binding FIXa and FX, was effective in HA patients with or without inhibitors,[18] although its combined use with bypass agents should be handled with caution.

Another approach is the inhibition of inhibitors of coagulation cascades, such as Concizumab (anti-TFPI by Novo Nordisk), that showed promising phase 1 results.[19] Fitusiran is a synthetic small interference RNA therapeutic molecule designed to suppress liver production of antithrombin. Its monthly subcutaneous administration improved TG and hemostasis.[20]

Future perspectives

The development of novel alternative therapeutics has not been studied in patients with other RBDs. Novel therapies are not expected to change the standard of care in RBDs that involve factors "downstream" from the coagulation cascade (e.g., dysfibrogenemia/FXIII deficiency) although, theoretically, there may be a potential role for them in the treatment of FVII/FXI/FX deficiency.

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