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Rare bleeding disorders-old diseases in the era of novel options for therapy

Tami Livnat, Assaf Arie Barg, Sarina Levy-Mendelovich, Gili Kenet *

The Israeli National Hemophilia Center and Thrombosis Institute, Sheba Medical Center, Tel Hashomer, and the Sackler faculty of Medicine, Tel Aviv University, Israel

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ABSTRACT

Rare diseases are defined as life-threatening or chronically debilitating diseases with a prevalence of less than one per 2000 according to the European Union or one per 1250 according to the USA. Congenital rare bleeding disorders RBD are reported in most populations, with incidence varying from 1 in 5000 (Hemophilia A), 1:30,000 (Hemophilia B) to much rarer (1:500,000 for FVII deficiency, 1–3 million for Prothrombin or FXIII deficiency). Acquired Hemophilia A is also a rare bleeding disorder with estimated frequency of 1 in million. Most RBDs are inherited as autosomal recessive (AR); however, heterozygous carriers with varying degrees of corresponding factor deficiency may render an unpredictable propensity for bleeding.

In patients with bleeding symptoms, laboratory assessment and especially molecular techniques currently enable accurate diagnosis and may provide tools for prenatal and family counseling. Currently hemostasis control is mainly based upon replacement of the missing coagulation factors (unless presence of inhibitors renders it impossible), however future gene therapy and disruptive, non-replacement alternatives may be promising for patients with RBD.

1. Introduction

Hemostasis is a dynamic process, which evolves in-utero. In response to vessel wall injury platelets, which initially attach to subendothelial collagen and von Willebrand factor (vWF), accumulate. Platelet activation, involving conformational changes of GPIIb/IIIa receptor and granule release leads to aggregation and rapid formation of a platelet clot. Sequential activation of a cascade of zymogen coagulation proteins to active serine proteases occurs and culminates in generation of thrombin, that ultimately activates more platelets, fibrinogen and other coagulation factors, in order to create stable blood clots [1–2].

With the many players involved in coagulation, it can be seen how the clinical bleeding phenotype can be modified by genetic interactions affecting the integrity of clot formation directly or indirectly [3].

Various bleeding disorders yield impaired thrombin generation (TG), which may be corrected by proper replacement therapy. Clinical symptoms may significantly differ among patients, however, the severe disorders tend to present early at the neonatal period.

Physiologic concentrations of coagulation proteins gradually increase during pregnancy and are lower in premature infants as compared to full-term babies or healthy children [4–7]. In the neonate, plasma concentrations of vitamin-K dependant coagulation factors (II, VII, IX, X) and contact factors (XI, XII, prekallikreine and high molecular weight kininogen) are about 50% of adult values [4–6]. Furthermore, the capacity of newborns to generate thrombin is reduced [8–9]. Yet, the hemostatic system is balanced by the protective effects of physiologic deficiencies of the inhibitors of coagulation, as well as by the decreased fibrinolytic capacity in infants [8–11].

Although laboratory diagnosis of coagulation disorders in infants may be difficult to establish, due to the need to adapt all coagulation assays and analytic instruments for small amounts of blood and the age-related interpretation required for test results [11], still it enables diagnosis, evaluation and treatment of symptomatic infants with hemostasis defects.

Rare diseases are defined as life-threatening or chronically debilitating diseases with a prevalence of less than one per 2000 according to the European Union or one per 1250 according to the USA [12]. Both hemophilia A (HA) and hemophilia B (HB), with reported prevalence of 1:5000 and 1:30,000 live male births, respectively, are the most frequent congenital rare bleeding disorders (RBD). RBD's are reported in most populations, with incidence varying from 1 in 500,000 for FVII deficiency to 1 in 2–3 million for Prothrombin or FXIII deficiency [13]. The European network RBD (EN-RBD) project confirmed that among screened populations FVII and FXI deficiency comprise 39% and 29% of RBD, whereas disorders of fibrinogen (8–9%), FXIII (6%), FV + FVIII deficiency (3%) and Prothrombin (1%) are rarer. Most RBDs are inherited as autosomal recessive (AR); however, heterozygous carriers may have varying degrees of corresponding factor deficiency that render an unpredictable propensity for bleeding. Naturally, consanguineous marriage may increase the expression of specific gene mutations among some populations [13].

* Corresponding author at: The Israeli National Hemophilia Center and Thrombosis Institute, Sheba Medical Center, Tel Hashomer 52621, Israel.
E-mail address: Gili.kenet@sheba.health.gov.il (G. Kenet).

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This review provides an overview of the etiology of rare bleeding disorders, either congenital or acquired, along with a concise review of their manifestations and updated diagnostic and treatment modalities.

1.1. Clinical symptoms and presentations

Severe bleeding disorders often present abruptly, in early life, with acute bleeding symptoms that may occur either spontaneously or following minimal trigger. Symptoms that may indicate the presence of a bleeding disorder and lead to its diagnosis in the perinatal period would be: bleeding into the scalp-forming cephalhematomas, injury related bleeding- following invasive procedures (e.g. circumcision) or intramuscular injections and sites of peripheral venipunctures and bleeding into the skin. Facial purpura following birth is usually associated with severe platelet dysfunction or thrombocytopenia. Oral mucous membrane bleeding is common for thrombocytopenic infants, however gum bleeding and epistaxis hardly ever present in neonates. Joint hemarthroses, typical for severe hemophilias, rarely occur before ambulation. Persistent oozing from the umbilical stump is typical for infants with defective fibrinogen production or function and FXIII deficiency.

Bleeding isolated to a single organ or system is more likely to occur due to a local cause rather than a hemostatic abnormality. Hemoptysis, hematemesis, gastrointestinal tract bleeding or hematuria- is rarely the presenting symptom of a bleeding disorder (in contrast, hematuria in neonates may be the presenting symptom of renal vein thrombosis). Nevertheless, hemostatic abnormalities may exacerbate those symptoms in sick children with acquired deficits, such as DIC, liver failure or vitamin-K deficiency.

A small proportion of infants with severe coagulation factor deficiencies present with intracranial hemorrhage (ICH) as the first manifestation of their bleeding tendency. Central nervous system (CNS) bleeding is reported in FVII, FXIII and FX deficiencies. The overall prevalences may range up to 25% in FXIII deficiency. It was also rarely observed in a fibrinogenemia, FII, FV and vitamin K-dependent coagulation factors deficiencies [14]. In contrast to the above, some patients with contact pathway deficiencies, e.g. FXI deficiency, may present only after adulthood, with post trauma or surgical bleeding, typical for tissues where high fibrinolytic activity prevails (e.g.: teeth extractions, urinary and prostate surgeries) [13].

In general, serious bleeding (e.g., ICH or musculoskeletal or umbilical cord bleeding) is rare in FV and FXI deficiencies, as is spontaneous bleeding in FXI deficiency. Bleeding phenotype is widely heterogeneous in FV, FVII, and FXI deficiencies and, in contrast to HA and HB, correlates poorly with factor activity levels. Combined FV and 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 in infancy or in early childhood with serious bleeding events, including ICH, as well as skeletal abnormalities, possibly due to defective γ-carboxylation of bone matrix proteins [15].

Women with RBD 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 (namely FXIII and FI) play in placental implantation and pregnancy maintenance [13,15].

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.

1.2. ICH

Intracranial hemorrhage (ICH) is by far the most devastating and often fatal event that occurs in patients with RBD. Survivors of ICH frequently have long-term consequences such as paralysis, seizures, cerebral palsy and other neurologic deficits. The signs and symptoms of ICH may be initially vague, often leading to a delay in diagnosis.

Intra ventricular hemorrhage (IVH) is rarely present at birth; however, 80–90% of cases among "healthy" infants (who do not have any RBD) occur before the 3rd day of life and 50% occur on the 1st day. ICH/IVH prevail among premature infants and recently it has been reported that neonates with ICH exhibit lower prothrombin levels as compared to controls [16–17]. As previously mentioned, severe defects in coagulation and hemostasis have also been implicated in ICH in term infants [15]. Severe FVII deficiency may present with serious bleeding events (e.g., ICH) in infancy [18], similarly, severe FII deficiency presents early in life with mucosal and musculoskeletal bleeding and ICH [19], FX and FXIII deficiencies are generally characterized by early onset of serious or life-threatening ICH or umbilical cord bleeding [20]. An analysis of prospective data collected from 580 neonates and toddlers aged 0–2 years with hemophilia enrolled in the surveillance project of the Centers for Disease Control and Prevention (CDC), showed that intra- and extra-cranial haemorrhages were the second most common presenting bleeding symptoms [21]. The overall incidence of ICH among patients with hemophilia is estimated as 1.9% with mortality rate of 19.6%, ICH rate after head trauma is reported to be 2% to 16%, and there is evidence that even after minor head trauma there is an increased risk of developing ICH [22–24]. A recent retrospective study collected data of CNS bleeding in 24 RBD patients with severe deficiency (36 episodes). A third of these experienced early bleeds (before 2 years of age) and in the majority (76%) bleeding was spontaneous. Six patients (25%) experienced a recurrence and two had more than one recurrence [25]. As consequences of CNS bleeding are extremely severe, increased awareness is required by clinicians around deliveries and after any head trauma in patients with RBD.

1.3. Laboratory diagnosis

The diagnosis of RBD is usually straightforward, requiring standard coagulation tests time prolongation, preceded by special assays for factors' activity. Naturally prolonged prothrombin time (PT) would lead to diagnosis of FVII deficiency whereas partial thromboplastin time (aPTT) prolongation may stem from low plasma coagulation factor VIII (FVIII), FIX, FXI, FXI. In case both tests are prolonged defects of fibrinogen, FV, FV + FVIII or prothrombin deficiency should be studied. Normal screening tests would not exclude FXIII deficiency [26] or rare platelet function disorders (e.g.: Glanzmann thrombasthenia- the latter should be diagnosed by platelet aggregometry, flow cytometry (FC) and proper molecular genetic studies). A stepwise approach to coagulation laboratory studies is presented in Fig. 1.

Interestingly, there is a heterogeneous association between coagulation factor activity level and clinical bleeding severity in different RBDs. A strong association is only observed in fibrinogen, FX and FXIII deficiencies. The European RBD network has reported that coagulation factor activity levels that were necessary for patients to remain asymptomatic were: fibrinogen, >100 mg dL (−1); FV, 12 U dL (−1); combined FV + VIII, 43 U dL (−1); FVII, 25 U dL (−1); FX, 56 U dL (−1); FXI, 26 U dL (−1); FXIII, 31 U dL (−1). Moreover, coagulation factor activity levels that corresponded with Grade III bleeding were: undetectable levels for fibrinogen, FV and FXIII, <15 U dL (−1) for combined FV + VIII; <8 U dL (−1) for FVII;<10 U dL (−1) for FX; and <25 U dL (−1) for FXI [20].

Notably, patients may also present with bleeding symptoms and a prolonged PTT due to presence of auto antibodies against FVIII. In these rare cases of acquired hemophilia, aPTT does not correct after mixing with normal plasma. When patient's plasma is incubated (2 h, 37 °C) with FVIII, its residual activity after 2 h defines FVIII inhibitor level, as measured by Bethesda units (1 BU inhibits 50% of FVIII activity under these conditions).

Lupus Anticoagulant (LA) can cause false-positive results in the inhibitor detection (Bethesda) assay. Although presence of LA is not