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ORIGINAL ARTICLE

Rare bleeding disorders

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Summary. Rare bleeding disorders (RBDs) include the inherited deficiencies of fibrinogen, factor (F)II, FV, FV+FVIII, FVII, FX, FXI and FXIII. There have been remarkable advances in understanding the molecular profiles that lead to each type of coagulation factor deficiency. However, as a consequence of their rarity, clinical data regarding the characteristics of bleeding symptoms and their management remain limited. The clinical manifestations in different RBDs are heterogeneous, and the residual plasma coagulant factor level does not always predict bleeding tendency. In this review, we describe the general features and recent advances in understanding three such deficiencies: FXI, FVII and fibrinogen deficiencies.

Keywords: factor VII, factor XI, fibrinogen, haemostasis

Introduction

Rare bleeding disorders (RBDs) represent 3% to 5% of all inherited coagulation deficiencies, and are usually transmitted as autosomal recessive traits [1,2]. They include inherited deficiencies of fibrinogen, factor (F) II, FV, FVII, FX, FXI, FXIII and combined FV and FVIII deficiencies (FV+VIII). Globally, RBDs have a variable distribution with a prevalence ranging from approximately 1 in 2 million for FII and FXIII deficiencies to 1 in 500,000 for FVII deficiency [1–4]. Despite their rarity, RBDs have been gaining increasing attention in both developing and developed countries where numbers continue to increase due to an expanding immigrant population. Due to the low prevalence of RBDs, data on the genetic, laboratory, and clinical characteristics of these disorders have been limited [5]. Scientific reports were usually limited to small groups of patients or even single cases. Hence, evidence-based guidelines for the diagnosis and management of this patient population are still lacking. However, several national and international registries dedicated to the study of RBDs are becoming increasingly available. Ongoing and future studies from these registries will hopefully fill the gap in knowledge concerning these orphan disorders. With this background, we herein highlight recent advances in understanding three such congenital RBDs: FXI, FVI and fibrinogen deficiencies.

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Factor XI deficiency

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FXI is stimulating current research interest both because of its minor role in haemostasis and also for the potential role of FXI inhibitors for prevention of thrombosis. An absolute deficiency of FXI in man is associated with a mild bleeding risk, such that individuals may be diagnosed incidentally or late in life, and the bleeding pattern is very different from severe deficiency of other coagulation factors (such as FVIII and FIX, or the rare factor deficiencies including FVII). Animal experiments have demonstrated that knock-out mice for FXI or FXII have no bleeding tendency and thrombosis is abolished, leading to the interesting proposal that FXI inhibitors in humans may prevent thrombosis without increased bleeding risk [6]. Humans with inherited FXI deficiency are protected against stroke [7], but not myocardial infarction [8], and have a reduced incidence of venous thrombosis [9].

FXI has a unique structure among coagulation factors as a dimer, and participates in coagulation by

reinforcement of the intrinsic pathway and inhibition of fibrinolysis. It is activated by thrombin [10] and may be important in low tissue factor environments [6]. Inherited factor XI deficiency is associated with a mild bleeding tendency (and an absence of spontaneous bleeding) which is not easily predicted from the FXI level [11]. Most individuals with severe deficiency (i.e. FXI level below about 15 IU/dl and two gene mutations) are at risk of bleeding. Bleeding characteristically occurs after accidents or surgery in areas of high fibrinolysis, particularly the mouth and genitourinary systems. Excessive bleeding may occur in individuals with mild as well as severe deficiency unrelated to the FXI level, suggesting that additional factors are implicated. Recent data from the European Network of Rare Bleeding Disorders (EN-RBD) confirmed this observation, by absence of correlation between FXI activity level and the severity of clinical bleeding [12]. There is increasing evidence that the overall balance of haemostasis is relevant, as has been found in von Willebrand disease [13]. It is likely that the interaction of platelets and other coagulation factors can modulate the bleeding risk. There is current interest in determining whether or not global tests of haemostasis such as thrombin generation tests and thromboelastography give more indication of the bleeding risk, but to date results are conflicting, which may be due to the lack of standardization of the test parameters [14].

FXI deficiency is particularly common in Ashkenazy Jews, but it is found in all racial groups. Founder mutations have been described in the French Basques and also in the UK. Mild deficiency is most commonly diagnosed after pre-operative coagulation screening, but it is important to consider screening women with menorrhagia [15]. Treatment should be tailored to the individual situation. Close supervision without specific replacement (with avoidance of medications that enhance bleeding risks) may be sufficient. Some forms of surgery have a lower risk of bleeding [16] in contrast to tonsillectomy and other surgery to the nose. Antifibrinolytic agents are very useful, particularly for menorrhagia, and are also sufficient for dental extractions even in severe deficiency [17]. Plasma (preferably pathogen-inactivated) is effective, with the disadvantage that large volumes may be required. Consideration can be given to starting an infusion the day before in people having elective surgery. There are also two FXI concentrates available in some countries. These are very effective in producing a predictable increase in FXI with a long half-life so that treatment may be given daily or on alternate days. The target level should not be too high, for example 30-40 IU/dl in severely deficient patients, and both products should be used with caution in patients with pre-existing thrombotic risk factors, as both products have been associated with an increased risk for thrombosis [11]. Individuals who develop anti-FXI antibodies (about a third of those with termination mutations [18]) do not necessarily have bleeding problems and can be treated for surgery with low doses of recombinant factor VIIa. This has also been suggested as primary treatment to avoid blood product use, particularly in those at increased risk of antibody development [19,20].

Factor VII deficiency

Angelika Batorova

Congenital FVII deficiency is a bleeding disorder caused by mutations in the gene coding for FVII (*F7*) with an autosomal recessive pattern of inheritance. Heterozygotes are usually asymptomatic, while homozygotes and compound heterozygotes develop hemorrhagic diathesis. However, in the last two the symptomatology is also variable, ranging from severe to mild or even asymptomatic forms, as the activity of FVII does not correlate well with bleeding tendency [12,21–23]. During the last decade, considerable advances have been made towards understanding the characteristics of FVII deficiency, thanks to extensive clinical studies in large cohorts of patients from the national and international multicentre registries [22–26].

The *F7* gene is located at chromosome 13q34 and comprises nine exons. To date, more than 130 mutations distributed throughout all the exons have been described [22,23,27–30] with a considerable proportion of mutations located on exon 8, which codes for the catalytic domain of FVII. The most prevalent are missense mutations, while splicing site and nonsense mutations are less frequent and small deletions are rare [22,28]. Mutations result in structural abnormality of FVII with decreased secretion or reduced function of protein [28,29]. Regional distribution of several gene defects was observed [22,23,28,31].

FVII deficiency is the most common RBD. The 2010 World Federation of Hemophilia (WFH) Annual Global Survey comprising data from 106 countries reported a total of 4938 persons with FVII deficiency, a number that represents 28% of all RBDs, excluding platelet disorders [32]. The survey demonstrated a wide variation in the prevalence ranging from 1:>2,000,000 (Japan, Sudan,Pakistan), through 1:500,000 (USA, Australia), 1:200,000 (Canada, Italy, Iran, Poland), 1:100,000 (UK, Croatia) to 1:60,000 (Ireland, Hungary). In Slovakia, the prevalence of persons with FVII level <10 IU/dl is 1:50 000; however, after including individuals with a FVII level ≤50 IU/dl, the prevalence becomes 1:10,000. Large variance in the prevalence may be influenced by the different criteria for patients' registration (threshold level of FVII, presence/absence of bleeding symptoms) among other regional differences.

Early reports of the disease suggested that intracranial bleeding is a common symptom of severe FVII deficiency [33]. However, variable symptomatology was

later described even in individuals with FVII levels <5 IU/dl [22–25] who experience a mild and asymptomatic phenotype in 58.7% and 14.7% of cases respectively [34]. The International registry of FVII deficiency (IRF7)/Seven Therapy Evaluation Registry (STER) [22,26] and the Greifswald registry [23], comprising a total of 687 and 717 individuals, respectively, represent the largest registries evaluating the phenotype-genotype relationship in FVII deficiency. The IRF7/STER Research Group proposed the classification of bleeding phenotype as haemophilia-like (severe symptoms), platelet-like (mild mucocutaneous bleedings, including menorrhagia) and asymptomatic [34].

Intracranial, gastrointestinal and joint bleeds classified as severe bleedings are invariably associated with a homozygous or compound heterozygous inheritance and FVII levels <5 IU/dl, without a clear relationship to the type of gene defect [22,23,34]. Menorrhagia is common in women; however, data on gynaecological and obstetric manifestations in FVII deficiency are generally limited [35,36]. Gynaecological bleeding in homozygous women with FVII levels <1.9 IU/dl is often severe and may be life-threatening, requiring frequent replacement therapy, red blood cell transfusions, hormonal therapy or surgical intervention. In this group of patients, the frequency of menorrhagia (92%), severe post haemorrhagic anaemia (46%), ovarian cysts (47%), hemoperitoneum (21%), hysterectomy/ovariectomy (61%) and postpartum bleeding (22%) [20, IRF7 unpublished data] is similar to that in type 3 von Willebrand disease (VWD) [35,36]. Thus, a scoring system designed for VWD, summarizing the types and severity of bleedings [37] may be appropriate for the classification of the severity of the bleeding phenotype in FVII deficiency as well.

Prevention and treatment of bleeding resides in the replacement of the missing factor with a need for repeated administration every 6-8 h because of the short biological half-life of FVII. Fresh frozen plasma (FFP) and prothrombin complex concentrates used in the past have limitations such as the risk of volume overload and the potential risk of thrombosis respectively [25,38]. Other options are plasma derived FVII concentrates (pdFVII) and recombinant activated FVII concentrates (rFVIIa), administered in initial doses of 10-30 IU/kg and 15-30 μg/kg respectively [25,26].

Several reports on surgical interventions under FVII replacement have been published [39–41], including continuous infusion of FVII concentrates [42] and rFVIIa [43]. A FVII level between 10-15 IU/dl has been considered to be a haemostatic minimum, however, neither a true minimum level nor the optimum duration of factor substitution in situations with a haemostatic challenge are known. A recent retrospective study showed that postoperative bleeding is related to the bleeding history, FVII level (threshold 7-10 IU/dl), and the type of surgery [44]. In the STER study, it was apparent that postoperative haemostasis can be secured by rFVIIa at a dose of at least 13 μg/kg administered three times per day. In patients with baseline FVII level <1 IU/dl and >10 IU/dl, the mean duration of postoperative replacement was 5.8 and 1.7 days, and the mean number of doses administered was 14 and 2.6 respectively [41].

The feasibility and efficacy of prophylaxis with pdFVII and rFVIIa have been demonstrated despite the short biological half-life of FVII. Long-term prophylaxis should be considered in all FVII deficient patients with a severe bleeding phenotype and recurrent bleedings [45].

Hereditary fibrinogen disorders

Philippe de Moerloose

Inherited disorders of fibrinogen are rare and can be subdivided into type I and type II disorders [46]. Type I disorders affect the quantity of fibrinogen in circulation: hypofibrinogenaemia is characterized by fibrinogen levels lower than 1.5 g/l, while afibrinogenaemia is characterized by the complete deficiency of fibrinogen. Type II disorders affect the quality of circulating fibrinogen: in dysfibrinogenaemia fibrinogen antigen levels are normal, while in hypodysfibrinogenaemia levels are reduced.

Afibrinogenaemia has an estimated prevalence of around 1:1,000,000 the and is increased in populations where consanguineous marriages are common. More than 80 distinct mutations, the majority in *FGA*, have been identified in patients with afibrinogenaemia (in homozygosity or in compound heterozygosity) or in hypofibrinogenaemia, since a large number of these patients are in fact asymptomatic carriers of afibrinogenaemia mutations [47]. A registry for hereditary fibrinogen abnormalities can be accessed at http://www.geht.org/databaseang/fibrinogen/. Causative mutations can be divided into two main classes: null mutations with no protein production at all and mutations producing abnormal protein chains. In the majority of patients with afibrinogenaemia or hypofibrinogenaemia there is no evidence of intracellular accumulation of the mutant fibrinogen chain. However, three mutations, all in *FGG*, are known to cause hypofibrinogenemia accompanied by hepatic storage disease [47,48].

Bleeding due to afibrinogenaemia usually manifests in the neonatal period but a later age-of-onset is not unusual. Intracranial haemorrhage is the major cause of death. Joint bleeding is less frequent than in patients with severe haemophilia [49]. There is an intriguing susceptibility of spontaneous rupture of the spleen. Menstruating women may experience menometrorrhagia. First trimester abortion is also common in afibrinogenaemic women. Moreover, antepartum and postpartum haemorrhage have been reported. Hemoperitoneum after rupture of the corpus luteum has been observed. Paradoxically, both arterial and venous thromboembolic complications are observed in afibri-

nogenaemic patients. These complications can occur in the presence of concomitant risk factors such as co-inherited thrombophilic risk factors or after replacement therapy. However, in many patients, no known risk factors are present. Hypofibrinogenaemia patients are usually asymptomatic with fibrinogen levels around 1.0 g/l, levels which are in theory high enough to protect against bleeding and to maintain pregnancy. However, they can bleed (as normal individuals) when exposed to trauma, or if they have a second associated haemostatic abnormality. Hypofibrinogenaemic women may also suffer from pregnancy loss. Recent data from the EN-RBD showed a strong association between coagulation factor activity level and clinical bleeding severity for patients with fibrinogen deficiency [12].

Replacement therapy is effective in treating bleeding episodes in congenital fibrinogen disorders [5,46,50]. Fibrinogen concentrates are safer than cryoprecipitate or FFP. Furthermore, more precise dosing can be accomplished with fibrinogen concentrates because their potency is known, in contrast to FFP or cryoprecipitate. The conventional treatment is episodic, in which fibrinogen is administered as soon as possible after onset of bleeding (treatment on demand). The other approach consists of giving either fibrinogen concentrates from an early age to prevent bleeding and, in case of pregnancy, to prevent miscarriage (primary prophylaxis) or after bleeding to prevent recurrences (secondary prophylaxis). Effective long-term secondary prophylaxis with administration of fibrinogen every 7-14 days has been described. Women with congenital afibrinogenaemia are able to conceive, but the pregnancy usually results in spontaneous abortion at 5-8 weeks of gestation unless fibrinogen replacement is given [51]. Oestrogen-progestogen preparations are useful in case of menorrhagia. Acquired inhibitors after replacement therapy have been reported in only two cases so far. As previously mentioned, one of the major complications is thrombosis. Some clinicians associate small doses of heparin or low-molecular weight-heparin with the administration of fibrinogen. In case of thromboembolic complications, direct anti-Xa or thrombin inhibitors can bind thrombus-bound thrombin, which is not the case with heparin. Thromboembolic complications are always difficult to deal with, since at the same time it is necessary to give anticoagulants but also fibrinogen preparations in severe fibrinogen disorders.

The second class of hereditary fibrinogen abnormalities are the type II disorders, i.e. dysfibrinogenaemia and hypodysfibrinogenaemia [46,47,52,53]. As in afibrinogenaemia and hypofibrinogenaemia, both are heterogeneous disorders caused by many different mutations in the three fibrinogen-encoding genes. Dysfibrinogenaemias and hypodysfibrinogenaemias are generally associated with autosomal dominant inheritance, caused by heterozygosity for missense mutations in the coding region of one of the three fibrinogen genes and so they are more frequent than type I disorders. Indeed, over 400 cases of dysfibrinogenaemia have been reported to date, with more than 40 distinct mutations identified (more than 60 distinct mutations in dysfibrinogenaemia and hypodysfibrinogenaemia combined). Missense mutations at residue *FGA* R35, which is part of the thrombin cleavage site in the fibrinogen α-chain, are the most common causative mutations accounting for dysfibrinogenaemia, found in approximately 40% of cases [47]. Most dysfibrinogenaemia mutant molecules are found in plasma at normal antigenic levels; thus they can be diagnosed by the combination of a prolonged thrombin time, normal levels of fibrinogen antigen, and low functional levels of fibrinogen.

Most cases are asymptomatic and are only identified as a result of routine coagulation screening. Approximately 25% of patients with dysfibrinogenaemia have a history of bleeding, and in approximately 20% a tendency towards thrombosis is observed [52]. Women with dysfibrinogenaemia can also suffer from spontaneous abortion. Some mutations in the Aα chain of fibrinogen are associated with a particular form of hereditary amyloidosis [54].

The gold standard for the diagnosis of dysfibrinogenaemia is the characterization of the molecular defect. Some mutations are predictive of the clinical phenotype: e.g. the R573C substitution in the Aα chain predisposes patients to thrombosis whereas mutations in the amino-terminal region of the Aα chain are associated with bleeding. These examples illustrate how determining the causative mutation can allow to take precautionary measures and guide treatment, which, however, should be based mainly on the personal and family history.

Conclusion

Knowledge regarding RBDs is expanding, and recent studies have established important milestones in understanding these rare disorders. However, several gaps in the literature persist and large prospective observational studies and clinical trials are needed to answer questions on the actual incidence and prevalence at birth; the incidence of bleeding episodes per year; the association between genotype, laboratory phenotype and clinical severity; the minimum amount of clotting factor concentrate to prevent bleeding; the effect and side-effects of treatment products; as well as harmonization between different antigen/activity assays. When such data become available, evidence-based guidelines for the diagnosis and management of RBDs will transform from a long-due quest to a reality.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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