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Rare bleeding disorders: a narrative review of epidemiology, molecular and clinical presentations, diagnosis and treatment

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ABSTRACT

Rare bleeding disorders (RBDs) are a heterogeneous group of disorders including different types of coagulation factor deficiencies. The disorders are inherited in an autosomal recessive manner with different frequencies varying from 1:500000 to 1:2000000. Patients affected with RBDs are presented with a wide spectrum of clinical manifestations ranging from mild to life threatening bleeding diathesis. These disorders are usually present in regions with high rate of parental consanguinity. Despite the rare incidence of RBDs, it is necessary for physicians to be aware of these disorders. Here we aim to have a comprehensive review on general features and also the recent advances in understanding of RBDs. For this review study we searched MEDLINE and Web of Science databases for English sources from 1990 to 2014, using the following keywords: rare bleeding disorder, rare inherited disorder, factor deficiency, structure, function, epidemiology, manifestations, laboratory analysis, diagnosis, mutation, treatment, management and also all the factor deficiencies which are considered as RBD. Knowledge towards RBDs is increasing, however, most of published data are limited to small group of populations or case reports. Therefore, there are still several questions on these rare disorders which need to be clarified through large prospective studies.

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Introduction

Rare bleeding disorders (RBDs) are a heterogeneous group of disorders that account for 3-5% of all inherited coagulation factor deficiencies. Most of these deficiencies were first described in 1940s or 1950s. RBDs occur due to a defect in one or more coagulation factors including fibrinogen, prothrombin, FV, combined FV and FVIII, FVII, FX, FXI and FXIII. These disorders are inherited in an autosomal recessive manner.[1,2] Their prevalence varies from 1:500000 to 1:2000000 in general population. Among all type of RBDs, FVII and FXI deficiencies which account for 37% and 23% of all cases, respectively are the most common (1, 3). The frequency of other types of RBD is as follow: fibrinogen (10%), Prothrombin (2%), FV (10%), FV+FVIII (3%), FX (9%), and FXIII deficiency (6%).[4] All type of RBDs except combined deficiency of FV and FVIII occur due to mutation in relevant coagulation factor gene. In combined FV+FVIII deficiency the defect results from the mutation in gene-encoding proteins involved in intracellular transport of these factors.[4, 5] Figure 1 has shown the worldwide distribution of rare bleeding disorders.

Considering the coagulant activity and antigenic level, RBDs classified in two types including type I and type II. The former is a quantitative defect that is characterized by reduced levels of coagulation factor while the latter as a qualitative defect is defined by normal coagulation factor level but reduced functional activity.[5] Another classification of RBDs is based on the association between factor level and the severity of clinical phenotype.[6] This classification is indicated in table 1. RBDs usually presented in areas that consanguineous marriage is common such as the Middle Eastern countries like Iran and Southern India.[1] Although RBDs are rare disorders, the expanding migration lead to an increasing number of affected individuals which therefore attracted more attention of both developed and developing countries. The perpetual need for replacement therapy and inevitable complications of each product imposes a heavy burden on countries where RBDs are more common.[3] These made RBDs an economic problem especially in developing countries where some of the newly produced factor concentrates are not available yet. Currently there are several registries studying on RBDs, but there are still limited data regarding different aspects of RBDs due to the rare prevalence. In the current study we aim to have a comprehensive review on general features and also the recent advances in understanding of RBDs. General characteristics of each RBD are summarized in table 2, providing a quick overview for readers.

Materials and Methods

In order to select relevant search keywords we used the Medical Subject Headings (MeSH) of the MEDLINE database. If appropriate terms were not available in MeSH then relevant non-MeSH keywords were used. Accordingly, we performed a search through MEDLINE and Web of Science databases using the following keywords: rare bleeding disorder, rare inherited disorder, factor deficiency, structure, function, epidemiology, manifestations, laboratory analysis, diagnosis, mutation, treatment, and management. Besides all the mentioned keywords we searched for all the factor deficiencies which are considered as RBD, separately. In addition, inclusion and exclusion criteria were defined by the specific limits included to the search strategy:

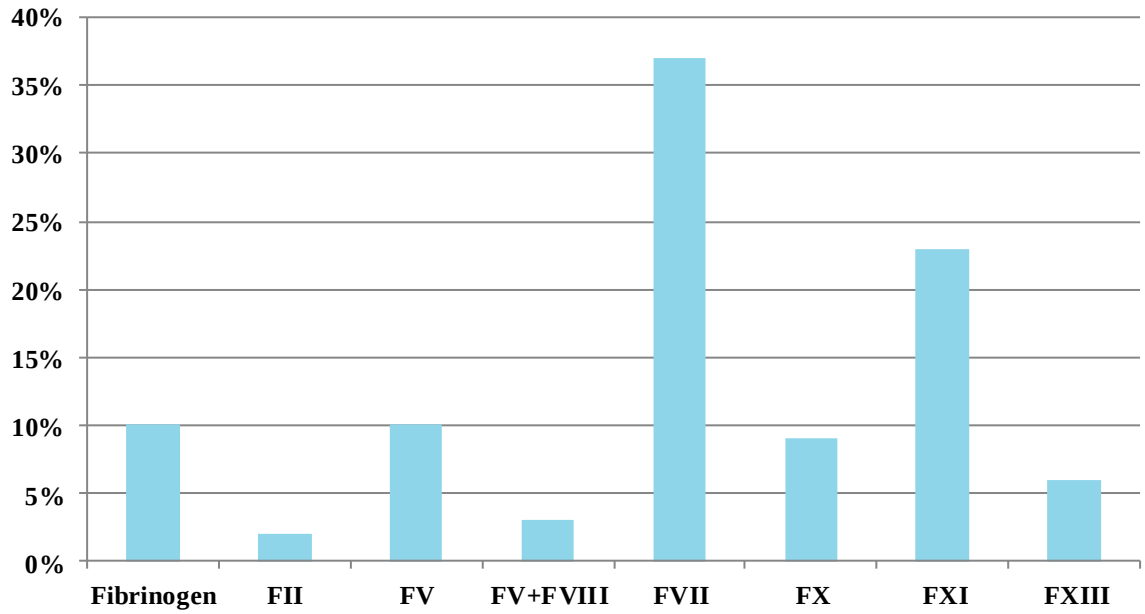

Figure1. Worldwide distribution of rare bleeding disorders

Table 1. Classification of the clinical severity of different RBDs based on the factor activity.[6]

Deficiency	Coagulant activity		
	severe	**moderate**	**mild**
Fibrinogen	Undetectable clot	0.1-1 g/L	> 1 g/L
FII	Undetectable activity	≤ 10%	> 10%
FV	Undetectable activity	< 10%	≥ 10%
FV+FVIII	< 20%	20–40%	> 40%
FVII	< 10%	10–20%	> 20%
FX	< 10%	10–40%	> 40%
FXIII	Undetectable activity	< 30%	≥ 30%

Table 2. General features of rare bleeding disorders

Deficiency	Prevalence	Gene (chromosome)	Routine coagulation testing	Available therapeutic choices
Fibrinogen	1 in 1 million	FGA , FGB , FGG (all on 4q28)	According to the type of deficiency is different (see text)	FFP Cryoprecipitate Fibrinogen concentrates Antifibrinolytic agents
FII	1 in 2 million	F2 (11p11 – q12)	Prolonged PT and APTT	FFP PCC
FV	1 in 1 million	F 5 (1q24.2)	Prolonged PT and APTT	FFP Antifibrinolytic agents
FV+FVIII	1 in 1 million	LMAN1 (18q21.3 – q22) MCFD2 (2p21 – p16.3)	Prolonged PT and APTT	FFP with/without FVIII concentrate or rFVIII
FVII	1 in 500,000	F 7 (13q34)	Prolonged PT but normal APTT (Exclusion of the vitamin K deficiency or other acquired causes are important)	FFP FVII concentrate FIX concentrate PCC rFVIIa Antifibrinolytic agents
FX	1 in 1 million	F 10 (13q34)	Prolonged PT and APTT (Exclusion of the vitamin K deficiency or other acquired causes are important)	FFP PCC Antifibrinolytic agents
FXI	1 in 1 million	F 11 (4q35.2)	Prolonged APTT but normal PT	FFP FXI concentrate Antifibrinolytic agents
FXIII	1 in 2 million	F 13A1 (6p24 – p25) F13B (1q31 – q32.1)	Normal PT, APTT, TT and BT. (Abnormal clot solubility test)	FFP Cryoprecipitate FXIII concentrates rFXIII

1. Only articles published in English were selected.
2. We defined a date restriction: from 1990 to 2014.

The sources published in the past seven years were preferred. No limitations to the type of studies were performed, but the preferences were given to the guidelines, narrative reviews, systematic reviews, epidemiological studies, and prospective studies.

Fibrinogen structure and function

Fibrinogen is a hexameric high molecular weight glycoprotein (330 KDa) which consists of two identical heterotrimers. This glycoprotein has 3 genes including FGA, FGB and FGG that all of them maps to chromosome 4q28. Each heterotrimer consists of three chains including Aa, Bb and c.[7] Fibrinogen structure is characterized by a central E domain connecting two D domains. Thrombin removes fibrinopeptide A (FPA) and B (FPB) at the N-terminal of the Aa and Bb Chains. Removal of these fibrinopeptides leads to production of soluble fibrin clot. The soluble clot is stabilized by activated factor XIII via formation of gamma–gamma dimmers and alpha polymers.[5,7]

Fibrinogen deficiency

Fibrinogen deficiency is an inherited bleeding disorder with an estimated prevalence of about 1 in 1 million in general population. The disorder occurs due to the mutations in the genes encoding fibrinogen chains including Aα, Bβ and γ. Fibrinogen deficiency is defined in different forms including quantitative or type I (afibrinogenemia and hypofibrinogenemia), qualitative (Type II) (dysfibrinogenaemia) or combined defects (hypodysfibrinogenemia). Afibrinogenemia and hypofibrinogenemia refer to complete absence and low levels of fibrinogen, respectively while dysfibrinogenaemia results from functional abnormalities of fibrinogen.[1, 8]

Clinical Manifestation

The common symptom in cases of afibrinogenemia is umbilical cord bleeding which is reported in about 85% of patients. Mucosal tract bleeding, central nervous system bleeding, impaired wound healing, hemarthrosis

and musculoskeletal bleedings are other clinical features. In addition, recurrent miscarriage, antepartum, and postpartum hemorrhage were also reported, suggesting that this factor has a significant role in implantation.[4, 9] Thrombosis was also rarely seen in the cases of afibrinogenemia. Although the mechanism of thrombosis is obscure but it seems that these patients can generate thrombin in first and second burst of thrombin generation. Clinical manifestations in individuals with hypofibrinogenemia are milder and usually occur following invasive surgery or major trauma. The clinical picture of dysfibrinogenaemia is different and most patients may have no symptoms. Some individuals present with bleeding tendency while others show signs of thrombosis. Patients usually have post surgery, post partum and post dental extraction bleedings. Lifethreatening bleeding episodes including umbilical cord bleeding and CNS bleeding occur rarely.[9, 10]

Molecular spectrum

Molecular finding is much more sensitive and in fact is a definitive diagnosis in all types of disorder. The majority of mutations in afibrinogenemia occur in FGA gene which most of them are deletions, nonsense, frame shift and spliced mutations. Among all mutations in FGA gene, large deletions (11 kb, 1238 bp and15 kb in the FGA gene) and frame shift mutations (IVS4+A>G and1138C>T in the FGA gene) are the most common.

Most of the patients affected with dysfibrinogenemia are heterozygote for

misssense mutation in one of the three genes (especially FGA) of fibrinogen. All fibrinogen variants that are identified to date are available on http://www.geht.org/databseang/fibrinogen .[7, 8]

Laboratory Diagnosis

Diagnosis of fibrinogen deficiency varies based on disorder. In cases with afibrinogenemia PT, PTT, TT and Reptilase time are prolonged.

In addition in most cases BT is also increased. The fibrinogen level in both antigenic and functional assay is undetectable (less that 0.1 g L).[9, 10]

In cases of hypofibrinogenemia, at first it is important to exclude acquired causes of fibrinogen deficiency. Although all coagulation tests are prolonged, TT is a more sensitive and more important test. The level of factor I is reduced in both antigenic and functional assays (between 0.5 g L1 and lower limit of normal range).[10, 11]

In dysfibrinogenemia TT is more sensitive. Reptilase time is also prolonged in this disorder but in some cases can be normal or reduced. Therefore, prolonged Reptilase time with normal functional fibrinogen, are indicative of dysfibrinogenemia.[10, 11]

Treatment

In patients with afibrinogenemia and hypofibrinogenemia replacement therapy is an effective treatment. The choices for replacement therapy are fresh frozen plasma (FFP), cryoprecipitate and plasma-derived fibrinogen concentrate. In addition in dental procedure the antifibrinolytic agent such as aminocaproic acid and tranexamic acid may be useful. The overall fibrinogen level must be maintained at 1.0 g/L, therefore, cryoprecipitate in dosage of 1 bag per 5 kg of body weight and based on clinical features and response should be continued by 1 bag per 15 kg of weight daily.

In cases with dysfibrinogenemia, dysfunctional fibrinogen interferes with infused factor therefore there is no precise guideline. The level of fibrinogen should be achieved above 1.0 g/L so according to clinical manifestation and response to replacement therapy, the repeated dose must be considered.[9, 10, 12]

Prothrombin structure and function

Prothrombin (FII), a vitamin K dependent plasma zymogene, is a 72 KDa single chain glycoprotein. Prothrombin consists of four domains: a Gla domain in the N-terminal, kringle 1 and kringle 2 domains and a catalytic serine protease domain that locates on the C-terminal.

On phospholipids surfaces, prothrombin monomer can be cleaved in Arg271 and Arg320 by the prothrombinase complex (including FXa, FVa, and $Ca2^{+}$) and convert to the active thrombin dimer (FIIa).[13]

Prothrombin deficiency

Congenital prothrombin deficiency was first described by Quick in 1947. It is regarded as the rarest inherited bleeding disorder which affects 1 in 2 million people in the general population. Prothrombin deficiency is an autosomal recessive disorder with two main types, type I or hypoprotrombinemia (concomitant reduction of enzymatic activity and antigen level) and type II or dysprothrombinemia (reduction of enzymatic activity but normal antigen level). Compound heterozygosity which is a combination of both states is also reported.[13, 14]

Clinical manifestations

Complete prothrombin deficiency is incompatible with life. Heterozygotes are usually asymptomatic or may represent with excessive bleeding after surgery and tooth

extraction. Homozygote deficiencies with < 10% activity are associated with bleeding which can be life-threatening. Soft tissue hematomas, easy bruising and hemarthrosis are the most frequent hemorrhagic events. CNS bleeding, epistaxis, menorrhagia and gastrointestinal bleeding are also reported. Bleeding phenotype of dysprothrombinemia is more variable and usually less severe than hypoprotrombinemia and many affected individuals are asymptomatic or represent with mild bleeding symptoms.[13- 15]

Laboratory diagnosis

In severe prothrombin deficiency both PT and APTT may be prolonged, but depending on the reagent, in mild deficiencies the results can be within the normal ranges. In such condition clinical presentations and family history should be considered and a specific factor II assay, commonly the one-stage clotting assay based on PT, is required to confirm the diagnosis.[13]

Molecular spectrum

Prothrombin gene with 21 kb is located on the chromosome 11(11p11). More than 50 mutations have been identified in the prothrombin gene so far of which 80% are misssense mutations. In dysprothrombinemia, misssense mutations may impair the binding site of FXa such as Arg457Gln and Arg271Cys, or may disturb the catalytic site of the prothrombin such as Arg418Trp mutation. In hypoprotrombinemia, nonsense mutations and small deletions are also described and mutations are often close to the Gla and kringle domains and the A chain. Prothrombin deficiency in combination with other vitamin K dependent factors can be caused by molecular defects of the gene encoding gamma-glutamyl carboxylase.[13, 15]

Treatment

Prothrombin levels of 25-30 IU/dl can establish normal homeostasis, but in excessive bleeding and major surgeries a higher level of prothrombin is required. Replacement therapy is necessary in homozygote patients and in the case of bleeding or in order to provide the prophylactic level before surgery. Prothrombin complex concentrates (PCC) are preferred product which are available as 3 or 4- factor concentrates (containing specific quantities of FII, FIX, FX and with /without FVII). Fresh frozen plasma (FFP) is an alternative choice, if PCC is not available.[15, 16]

Factor V structure and function

Blood coagulation factor V (FV) is a high molecular weight glycoprotein (330 KDa) that is known as proaccelerin or labile factor. The gene of this factor maps to 1q24.2 chromosomal region and covers a genomic region of 74.5 kb. Human FV gene consists of 25 exons which form six domains (A1, A2, B, A3, C1 and C2), similar to coagulation FVIII (17). This factor has 40% identity with FVIII and the only domain of FV that has no important similarity with FVIII is domain B. Factor V takes part in coagulation cascade as a nonenzymatic cofactor for prothrombinase complex. FXa cleaved FV at three arginine residues including Arg709, Arg1018 and Arg 1545. With these cleavages FV missed the B domain and converted to FVa. FVa with FXa assemble a complex on phospholipid membranes and thereby lead to a 300000 fold increase in the activation of prothrombin. Moreover, it has an essential role in down regulation of coagulation factor VIII (FVIII) via enhancing the effect of activated protein C. Therefore it participates in both procoagulant and anticoagulant pathways.[17, 18]

FV deficiency

Factor V deficiency is a rare bleeding disorder with a frequency of 1 in 1,000,000 in general population. This disorder is classified in two types as follow: (a) type I deficiency or CRM-(cross reactive material negative) with unmeasurable level of function and antigen. (b) Type II deficiency or CRM+ (cross

reactive material positive) with unmeasurable level of function but normal level of antigen. This disorder based on the FV level is classified in mild, moderate and severe forms.[19]

Clinical manifestations

Mucosal tract bleeding is reported as the main clinical manifestation of this type of RBD. Epistaxis, gingival bleeding and menorrhagia account for 60% of clinical features. Post traumatic bleeding and post-surgery bleeding are other bleeding events. Hematomas and hemarthrosis are approximately reported in 25% of affected individuals. Life-threatening clinical features including gastrointestinal tract bleeding and central nervous system hemorrhage are rarely seen in patients.[13, 18]

Molecular spectrum

Among all rare bleeding disorders FV deficiency has more than 70 mutations while there is no common mutation. The reported mutations are small insertion/deletion, missense mutations, nonsense mutations and splicing defects. The first mutation described in this disorder is FV-New Brunswick (Ala221Val). This mutation causes instability of FV. The only mutation that repeatedly found in Italian population is Tyr1702Cys that indicates significant allelic heterogeneity of FV deficiency.[13, 20]

Laboratory diagnosis

The diagnosis of factor V deficiency is based on routine laboratory coagulation tests including PT, PTT and TT. The prolonged PT and PTT but a normal TT may be an indication of FV deficiency. FV antigen levels and FV clotting activity are evaluated by sandwich enzyme immunoassay (EIA) and one stage coagulation assay based on PT, respectively. In addition the activity of Factor VIII needs to be investigated to exclude the combined deficiency of factors V and VIII.[13, 20]

Treatment

Due to lack of FV concentrate, Fresh Frozen Plasma (FFP) preferably virus-inactivated is the only option for treatment of patients worldwide. The FV level should be achieved in 15 IU/Dl by dose of 15 to 20 mL/kg. This dosage is continued by small amounts of 5 mL/kg every 12 hours. In addition, antifibrinolytics including epsilon-aminocaproic acid or tranexamic acid with specific dosage based on clinical features may be needed in some cases such as menorrhagia.[12, 13]

Combined FV and FVIII deficiency

This hemorrhagic disorder was first described by Oeri J,et al in 1954. This disorder had a heterogeneous prevalence worldwide. The precise incidence is unclear but an incidence of 1 per 1000000 was reported for factor V and factor VIII deficiency (F5F8D). The highest prevalence of disorder was reported in some Iranian and Jews with a ten-fold increase compared to general population. A single mutation causes simultaneous deficiency of both factor V and factor VIII, resulting in a drop in plasma level of both factors usually between 5 to 20 percent. Simultaneous deficiency in FV and FVIII also can arise from coinheritance of genetic defects in two separated genes encoding FV and FVIII.[21, 22]

Clinical manifestations

Mild to moderate bleeding tendency was observed in patients affected by recessive F5F8D because the lowest level of both factors is not usually less than 5% and this factor level is sufficient for prevention of severe life threatening bleeding episodes. Epistaxis and gum bleeding are the most common clinical presentations among patients with F5F8D. Menorrhagia, post-dental extraction bleeding and postpartum

haemorrhage were also reported commonly in these patients. Excessive bleeding after circumcision is a common bleeding diathesis among male with F5F8D but amazingly this was not observed in some ethnics of Jews.[21-23]

Laboratory diagnosis

Diagnosis of patients with F5F8D can be performed by routine coagulation tests alongside the factor activity assays for both factor V and factor VIII. Clotting Time (CT), Bleeding Time (BT) and platelet count are normal in F5F8D patients while both prothrombin time (PT) and activated partial thromboplastin time tests (APTT) are abnormal. Factor assays for both factor V and factor VIII is necessary and based on factor assays, patients divide in three groups of mild (>40%), moderate (20%-40%) and severe (<20%).[6]

Molecular spectrum

This rare bleeding disorder is caused by mutations in lectin mannose binding protein 1 (LMAN1) or Golgi intermediate compartment (ERGIC-53) or multiple coagulation factor deficiency 2 MCFD2 genes. Most causative mutations of F5F8D patients are located in LMAN1 gene except in Indian population while MCFD2 gene involves a large number of causative mutations. More than 50 different mutations were reported in these two genes and LMAN1 gene involved approximately 70% of these mutations. The spectrum of mutations is heterogenic even in patients with same ethnicity. For example, in Iranian patients, frameshift mutations of exon 1 of LMAN1 gene were reported commonly but mutations in exons number 5, 7, 8, and 9 were also reported with some intron mutations.[21, 24]

Treatment

Because of mild to moderate bleeding tendency in patients with F5F8D, patients usually do not require regular prophylaxis but in cases with severe life threatening bleeding diathesis, regular prophylaxis should be considered. To date, there is not any concentrate for replacement of factor V and Fresh Frozen Plasma (FFP) is the only available therapeutic choice. However, a wide choice is available for FVIII replacement including recombinant FVIII, FFP and FVIII concentrate. Thus, on demand, prophylaxis therapy can be performed by FFP alone or in combination with other sources of FVIII. The aim of replacement therapy varies according to patients bleeding episodes, as in minor bleeding a 30–50 IU dL^{-1} of plasma FVIII level is required while in major bleeding 50–70 IU dL^{-1} is preferred.[13, 25].

FVII structure and function

Coagulation factor VII is a glycoprotein with molecular weight of 50 KDa that circulates in plasma in two forms. This glycoprotein is present in large amount in a single chain of inactive form and also in smaller amounts in active form. The active form of this glycoprotein contains two chains including light chain with 152 residues and heavy chain with 254 residues that are linked to each other by disulfide bond.[26] The light chain contains the gamma-carboxyglutamic acid (Gla) domain and also epidermal grows factor domains while the heavy chain contains catalytic domains. The gene of this factor maps to 13q34 chromosomal region and covers a genomic region of 12 kb. FVII gene (F7) consists of 9 exons, encoding a mature protein with 406b amino acids. Tissue actor as a cofactor forms a complex with FVII at site of injury; therefore, activated FVII initiates the coagulation cascade by auto activation and also by other factors including FIXa and FXa.[26, 27]

FVII deficiency

FVII deficiency is the most common type of rare bleeding disorders with an estimated frequency of 1:300000 to 1:500000 in general

population. This disorder is not associated with complete absence of FVII because it is not compatible with life.[13]

Clinical manifestations

Mucousal-type bleeding including gum bleeding and epistaxis are the most common clinical features in this disorder. Menorrhagia and iron deficiency anemia are prevalent in women with FVII deficiency. CNS bleeding is another common feature in these patients which is reported in 15 to 60% of affected individuals. Hemarthrosis, muscle haematoma and gastrointestinal bleedings are also reported in several cases with FVII deficiency. In addition, in presence of surgery and replacement therapy, thrombosis is reported in approximately 4% of cases.[13, 28]

Laboratory analysis

The diagnosis of FVII deficiency via laboratory analysis is based on prolonged PT and normal APTT tests. The prolonged PT is corrected by 50:50 mixing with normal plasma. The important point in diagnosis of FVII deficiency is to exclude the acquired causes of coagulation factor deficiency and also vitamin K deficiency. Based on FVII coagulant (FVII: C) levels, the INR is prolonged between moderate (1.5 to 1.8) to high (>2.0). To confirm FVII deficiency, the FVII: C is also measured by one stage PT-based assay. FVII antigen is measured via enzyme-linked immunosorbent assay (ELISA) or immunoradiometric assay (IRMA).[13, 29]

Molecular spectrum

DNA sequencing of coding regions in different patients with FVII deficiency results in characterization of various mutations. Among all reported mutations missense changes are the most common that account for 70 to 80% of all cases. Splicing- site changes are also reported in many cases while nonsense and small deletions are rarely seen. The misssense Ala294Val mutation and single nucleotide deletion 11125delC was reported in significant number of individuals with FVII deficiency especially in central Europe. It seems that each geographical region especially countries with high frequency of consanguineous marriages have their own mutational spectrum. With genotyping of whole gene we could find the causative mutation that is a key step in diagnosis of disease and more importantly in prenatal diagnosis.[13, 28]

Treatment

Different options for management of this disorder are available. Fresh Frozen Plasma (FFP) is widely used either by itself or in combination with FVII concentrate. But in cases that prolonged administration is needed, fluid overload is inevitable.

Other choices in management of individuals with FVII deficiency is FIX concentrate and prothrombin complex concentrate that contain FVII, FIX, and FX. Unfortunately, these concentrates are associated with risk of arterial and venous thrombosis, therefore, should be avoided in patients with conditions including liver disease, major trauma, antithrombin deficiency and also neonate with immature liver.

Factor VII concentrate is another option which is widely and successfully used in management of different cases with spontaneous bleeding. Recombinant factor VIIa is also used in management of individuals with factor V deficiency which has a shorter half-life compared to plasma FVII. As in FV deficiency tranexamic acid is an effective treatment during menstrual period in women suffering from menorrhagia.[13, 29]

Factor X structure and function

Factor X (FX) is a vitamin K dependent factor which is synthesized in the hepatocytes as a single-chain precursor, but circulates in

plasma as a two-chain glycoprotein with a molecular weight of 59 KDa. FX consists of a heavy chain with 306 amino acids and a light chain with 139, which are linked together by a disulfide bond. FX is the first zymogene in the common pathway of coagulation cascade which can be activated by two distinct complexes, including tissue factor/FVIIa or FIXa/FVIIIa complexes, on the phospholipid surfaces and in the presence of calcium ions. Activated FX is the most important physiological activator of prothrombin.[30, 31]

FX deficiency

Congenital FX deficiency was first identified by two independent groups, Tulfer et al. in 1956 and Hougie et al. one year later. The disorder inherited in an autosomal recessive pattern and has an estimated prevalence of 1 in 1 million in general population. The incidence of heterozygosity for FX deficiency is about 1 in 500 individuals. There are two main types of congenital deficiency including stuart like or type I (concomitant reduction of enzymatic activity and antigen level) and power like or type II (reduction of enzymatic activity but normal antigen level). Acquired FX deficiency secondary to amyloidosis is also described.[13, 31, 32]).

Clinical manifestations

FX deficiency may present at any age and severe deficiencies can present in neonates with umbilical cord bleeding. The most frequent bleeding diathesis in FX deficient patients is mucocutaneous bleeding in particular epistaxis which is observed in all severities of deficiency. Other mucosal-type bleeding occurs mainly in patients with severe deficiencies. Hemarthrosis, excessive postoperative hemorrhage and CNS bleeding have also been reported in severe deficiencies. FX deficient women may suffer from uterine bleeding, fatal loss and post partum hemorrhage. About 10-75% of women with severe deficiency are reported to have menorrhagia.[31, 32]

Laboratory diagnosis

A prolonged PT and APTT values besides clinical presentations and a family history can lead to a suspicion of FX deficiency. This probability is confirmed by measuring plasma FX levels, which is possible by using different assays including the one-stage PT/APTT-based assays, chromogenic assay, the assay employing Russell viper venom (RVV), and immunological assay. Before the definite diagnosis, vitamin K deficiency or other acquired causes are important to be excluded [33].

Molecular spectrum

The gene encoding FX with 22 kb long is located on the chromosome 13 (13q34-ter) and 2.8 kb downstream of the F7 gene. The earliest molecular defect involving F10 gene was first reported in 1985 by Scambler and Williamson. To date more than 105 mutations are reported in FX deficient individuals. Missense mutations are the most frequent cause of congenital FX deficiency. Nonsense mutations and deletions have also been reported in few cases. Furthermore, the mutations are almost private and in the entire group of misssense mutations only a few have been recurrent and found in more than one family from the same geographical area. The most common sites of mutations have been localized to the exon 8. [31, 32]

Treatment

Topical therapies and antifibrinolytic agents may be the only treatment in many cases with minor bleeding symptoms. For providing local homeostasis, fibrin glue may be helpful. The requisition for replacement therapy depends on particular hemorrhagic episode. To date no purified FX concentrate is available and Fresh Frozen Plasma (FFP) or prothrombin complex concentrates (PCC) can be applied as a source of FX. FX levels of 10-

20 IU/dl are described as sufficient for normal homeostasis and even in the immediate postoperative period.

In case of mucosal bleeding, a 5% solution of Tranexamic acid can be used as a mouthwash every 8 hours. In cases with acquired FX deficiency secondary to amyloidosis, rVIIa has been used successfully.[13, 33]

Factor XI structure and function

Factor XI (FXI) is a 160 KDa hemodimer, consisting of two disulfide-linked subunits. Each subunit, with 607 amino acid length, contains four apple domains in the N-terminal (A1-A4) and a C-terminal catalytic domain. The apple domains belong to the PAN domain family and are homologous with N-terminal domains of hepatocytes growth factor and plasminogen. A disk structure formed by these domains allows FXI bind to platelets, high molecular weight kininogen (HMWK) and FIX. In the coagulation cascade, FXI is activated by FXIIa or thrombin through a cleavage in the Arg369-Ile370 bond. Activated FXI, in turn, leads to the activation of FIX Which is followed by subsequent reactions of fibrin formation FXI is a critical factor in tissues with high fibrinolytic activity in order to retain clot integrity.[13, 34]

FXI deficiency

FXI deficiency, sometimes called hemophilia C, was first described in 1953 by Rosenthal as an autosomal recessive bleeding disorder. It has an incidence of about 1 in 1 million in general population with a higher prevalence in Ashkenazi Jews. It is reported that the rate of heterozygosity is 1 in 8 individuals and of homozygosity is 1 in 190 in this population.[34, 35]

Clinical manifestations

Bleeding tendency in FXI deficiency is unpredictable. Studies show that it is not associated with the plasma level of FXI coagulant activity and the FXI antigen. It might be due to probability that the risk of bleeding is more dependent on the amount of FXI in the platelet storages than the plasma levels. Furthermore, the bleeding phenotype may be attenuated or exacerbated by biological or environmental effects.[35] Spontaneous hemorrhage is not a common feature of FXI deficiency. Bleeding is more common after trauma or surgery particularly in sites of mouth, nose and genitourinary tract which are known to have high fibrinolytic activity. However, bleeding after orthopedic and gastrointestinal operation and circumcision is rare. Menorrhagia, epistaxis and easy-bruising are also common findings. Postpartum hemorrhage is reported with 20 % frequency. Severe deficiency with a level of < 15-20 IU/dl has a high risk of post-operative hemorrhage and partial or mild deficiencies with 20-65% are usually assymptomatic or have a lower risk of post-operative hemorrhage. The onset of clinical presentation is in the late childhood or early adulthood.[35, 36]

Laboratory Diagnosis

Usually screening tests will show an isolate prolongation in APTT. Considering the variable sensitivity of different partial thromboplastin reagents, the reference ranges should be established by each laboratory. The APTT result of almost all patients with severe FXI deficiency is more than two standard deviations above the normal mean, while heterozygotes may exhibit normal or slightly prolonged values. In cases with clinical suspicion, a positive family history or a prolonged APTT value, a specific assay to measure FXI activity is crucial. Further investigations may be required to exclude FXI inhibitors or lupus anticoagulants.[37]

Molecular spectrum

To date 152 mutations have been reported in the F11 gene which is located on chromosome

4q35.2. The underlying gene mutations are almost different in different populations. Three mutations were first described in Ashkenazi Jews: mutation at a splice site of the last intron (type I), Glu117stop mutation (type II), and phe283leu (type III). Type III mutation is exclusive to this population while type II is also found in Iraqi Jews and Arabs. Cys38Arg and Cys128Ter are considered as founder mutations in Basques (in France) and the UK, respectively. Accordingly the racial background of the patient can be quite helpful to determine the probable molecular defect. Direct sequencing of the FXI gene is now the preferable method for the mutation detection.[13, 37]

Treatment

Appropriate management of surgery and trauma is an important issue in FXI deficient individuals. Fresh frozen plasma (FFP) was widely used since specific FXI concentrates became available in 1980s. These new products allow patients to gain sufficient amount of FXI in a smaller volume and a shorter infusion time without unnecessary increase in other coagulation factors. Later it was revealed that there is a risk of thrombotic events with these products. For many cases undergoing minor procedure or with mild deficiencies, antifibrinolytic agents, such as tranexamic acid and ε-aminocaproic acid are usually effective without the need for factor replacement therapy.[13, 38]

FXIII structure and function

Factor XIII is a protransglutaminase enzyme that consists of two subunits including FXIII-A and FXIII-B, and circulates in plasma in tetrameric form (A2B2). The potentially active FXIII-A is a single chain polypeptide with 731 amino acids and 83 KDa molecular weight that carries the catalytic part of enzyme. This subunit is synthesized in bone marrow originated cell. The gene of FXIII-A is located at chromosomal region 6p24-24, and covers 160 kb with 15 exons. The gene of FXIII-A encoded a protein that contains 6 domains as follow: activation peptide, catalytic core region, catalytic core region and two β-barrels. FXIII-B is a single chain polypeptide which contains 641 amino acids with 80KDa molecular weight and is produced in hepatocytes. The gene of this subunit is located on 1q31-32 chromosomal region and spans 28 kb with 12 exons. This gene encoded a protein with ten consensus repeats named sushi-domain repeats.[39]

FXIII has an essential role in final step of coagulation cascade via stabilizing the fibrin clot. Thrombin turns FXIII to active form by a cleavage at Arg37-Gly38. The activated FXIII acts a transglutaminase and catalyses the gamma-epsilon-lysine bond between fibrin chains. These bonds form between Gln 398 in one molecule and Lys406 in another fibrin and, therefore, stabilized the fibrin clot.[13, 39]

FXIII deficiency

FXIII deficiency is an extremely rare bleeding disorder with a prevalence of 1:2000000. This type of RBD is also frequent in regions with high rate of consanguinity such as south east of India and Iran. Sistan and Baluchistan located in south east of Iran has the highest prevalence of this disorder around the world. This province has a population of about 2700000 of whom 350 individuals are affected with FXIII deficiency.[40]

Clinical manifestations

Umbilical cord bleeding is the most common clinical features in individuals affected with FXIII deficiency which is reported in more than 80% of the cases. This feature occurs a few days after birth and is a life threatening event especially in homozygote patients. CNS bleeding is another life threatening clinical manifestation, observed in approximately 30% of the patients. Compared with other rare bleeding disorders FXIII deficiency has the

highest frequency of CNS bleeding. In addition CNS bleeding is considered as a major cause of death in affected individuals. Delayed wound healing is another common bleeding feature, seen in almost 14-29% of the patients. Recurrent miscarriage is a common complication which threats the life of women affected with FXIII deficiency because this coagulation factor is necessary for attachment of the cytotrophoblasts after invading to the endometrium. Other bleeding diatheses are post trauma subcutaneous bleeding, gum bleeding, post dental extraction bleeding, muscle and joint bleeding.[41]

Laboratory analysis

The diagnosis of FXIII deficiency is based on normal results of routine clotting laboratory tests including PT, aPTT, fibrinogen level, platelets count and bleeding time (BT). With normal result of these testes qualitative and quantitative assays are necessary. Fibrin clot solubility in solution of 5 M urea or 2% acetic acid (or1% monochloroacetic acid) as a qualitative test is the most common screening test. The positive result is achieved when the activity of FXIII in plasma is zero or close to it. The positive result of qualitative tests required quantitative analysis of FXIII activity. Different quantitative assays are now available such as photometric methods that measure the activity of FXIII based on ammonia release in the transglutaminase reaction. Amine incorporation assay is another method that works based on measuring the amines covalently cross-linked to a protein substrate. Fluorometric assay is also a method considering isopeptidase activity of FXIIIa. The last method is an antigenic ELISA technique that evaluates concentrations of the A and B subunits.[13, 42, 43]

Molecular spectrum

Factor XIII deficiency occurs due to different mutations in the genes of factor XIII A or B subunits. Among these two subunits most of mutations are reported in FXIII-A which are associated with significant clinical manifestations.

Like most rare bleeding disorders missense mutations are the most common and account for approximately 50% of all reported mutations. Other mutations including frameshift mutations, splice site substitutions and nonsense mutations have also been reported. All mutations which are reported until now are available in Factor XIII Registry Database website (http://www.f13-database.de). Among all mutations and polymorphisms which are recognized so far, Val34Leu (exon 2), Tyr204Phe (exon 5), Pro564Leu, Pro(CCA)331(CCC)Pro (exon 8), Val650Ile ,Glu(GAA)567Glu(GAG) (exon 12)and Glu651Gln (exon 14) are the most common in FXIII-A. In subunit B, His95Arg and C29759G changes in intron K29756 are the two common polymorphisms.[41, 44]

Treatment

Different options are available for treatment of bleeding episodes in FXIII deficiency including Fresh Frozen Plasma in doses of 10 mL kg^{-1} in 4–6 week intervals, cryoprecipitate in doses of 1 bag per 10–20 kg every 3–4 weeks and pasteurized FXIII concentrates (about 240 units/vial). Among all these options FFP and FXIII concentrates are preferred. Fibrogammin HS® is the first FXIII from human source which is originated from placenta. Later Fibrogammin HS® was replaced by plasma extracted FXIII concentrates [Fibrogammin P® (CSL Behring, Marburg, Germany) and FXIII-BLP® (Bio-Product Laboratory, Elstree, United Kingdom)]. In addition, recombinant FXIII is now available (Novo Nordisk, Bagsvaerd, Denmark).[13, 42]

Conclusion

Despite the rare incidence of RBDs, it is necessary for physicians to be aware of these disorders especially if working in regions with a higher prevalence of RBDs or with high rate of consanguinity. Knowledge towards different aspects of RBDs is increasing and there are several studies reporting the associated clinical and molecular presentations, diagnostic procedures and management. However, most of the published data are limited to small group of populations or case reports. Therefore, there are still several questions on these rare disorders which need to be clarified through large prospective studies by national and international registries. For example, the exact prevalence of RBDs in different populations, the association between clinical phenotype, genotype, and laboratory results, efficacy and complications of each therapeutic product and the minimum required factor concentrates to prevent bleeding are issues which remained unknown.

Conflict of Interest

None declared.

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