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ORIGINAL ARTICLE

Brief Overview about Inherited Rare coagulation disorders

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ABSTRACT

Background: Numerous rare congenital bleeding disorders include fibrinogen and prothrombin deficiency as well as factor (V, VII, VIII, XI, X, and XIII) deficiency. In the general population, the severe variants of these illnesses are hereditary and possess a frequency that falls somewhere between one in every two million for factor XIII and one in per half a million for factor VII. Patients who have rare congenital bleeding disorders may exhibit a broad range of symptoms, from relatively mild subcutaneous bleeding to potentially life-threatening hemorrhages for example in the central nervous system. The majority of treatment for these disorders when specific plasma-derived or recombinant products are available is to replace the missing factor. Diagnosing and treating rare congenital bleeding disorders can be challenging due to the wide variety of symptoms they manifest in patients. Patients with rare inherited bleeding diseases must be closely monitored at specialized hemophilia treatment centers once they are diagnosed, due to the unique difficulty of their therapy. More research is required to improve the worldwide care for individuals with rare inherited bleeding diseases, despite the fact that a lot has been learned about their frequency, symptoms, and genetic characteristics in the past ten years.We aimed at this review to give a brief overview about Inherited Bleeding Disorders.

Keywords: Inherited Bleeding Disorders, Rare, coagulation disorders.

INTRODUCTION

The main way that rare inherited bleeding disorders (RBDs) are passed down from generation to generation is through autosomal recessive inheritance. Congenital deficiency of vitamin K-dependent factors (VKCFDs) is one of these illnesses. Other coagulation factors that can be lacking include fibrinogen, factor II, factor V, combined FV and FVIII, factor VII, factor X, factor XI and factor XIII. In certain cases, such as dysfibrinogenemia and FXI, autosomal dominant inheritance is possible. In most populations, RBDs are recorded. With FVII deficiency, the frequency of homozygous or doubly heterozygous RBDs is 1 in 500,000; with prothrombin and FXIII deficiencies, it rises to 1 in 2–3 million. A higher relative frequency of certain mutant genes is associated with communities that practice more frequent forms of consanguineous marriages [1].

Classification

Because RBDs are so rare, researchers have paid less attention to studying their causes and pathogens, and it has been difficult to

describe their natural history and variations. Any RBD patient may have a wide range of bleeding symptoms, from minor traumatic episodes to life-threatening hemorrhages that start at birth or develop over time. Although some deficiencies are more likely to experience bleeding because to leftover coagulant activity, this is by no means always true. The EN-RBD was the first to establish a link between clinical RBD bleeding severity and residual coagulant activity; the study included 489 patients from 13 different treatment facilities across Europe. Location, possible clinical significance, and the presence or absence of a spontaneous, trauma-induced, or drug-induced bleeding trigger were used to categorize clinical bleeding events into four severity levels [2].

Fibrinogen, factor II, FV, FV + FVIII, FVII, FX, FXI, and FXIII deficiency are among the rare hereditary bleeding disorders that make up 3-5% of all inherited deficits of coagulation factors. These disorders are often passed down through families in an autosomal recessive fashion. Worldwide, their distribution varies; the most prevalent kind, FVII deficit, affects one in half a million people, while the rarest forms, FII and FXIII deficiencies, affect one in two to three million people. There have been reports of rare bleeding problems in the majority of populations, with a higher incidence in societies where marriages between relatives are widespread. While the specifics of bleeding patterns vary greatly among rare bleeding disorders, it seems that congenital hemophilia is more common than these disorders when it comes to severe bleeding affecting the central neurological and musculoskeletal systems [3].

Thrombin time (TT), activated partial thromboplastin time (APTT), and prothrombin time (PT) are the most reliable coagulation screening tests for diagnosing uncommon congenital bleeding disorders in individuals who have a personal or family history of bleeding. Coagulation factor assays can pinpoint the precise factor deficiency if aberrant screening test results are detected [4]. The molecular diagnosis may be provided after a search for mutations in the genes that encode the relevant coagulation factors. Antenatal and pre-implantation genetic testing is particularly vital in nations with high prevalence of consanguinity and relatively rare bleeding disorders [5].

Fibrinogen (FI) deficiency

The glycoprotein FI, which has a molecular weight of 340 kDa, is produced by the liver. The plasma concentration of this clotting factor ranges from 1.5 to 3.5 g/L, and its half-life is around four days. Each half of the FI molecule contains a trimer of different polypeptide chains known as Aα, Bβ, and γ, and the two halves are identical. In a 50 kilobases (kb) region on chromosome 4, in the sequence from the centromere to the telomere, are clustered together the three genes that code for FI Bβ (FGB), Aα (FGA), and γ (FGG). Fibrinogen (FI) is proteolytically cleaved by thrombin, which releases fibrinopeptides A and B. These, in turn, produce fibrin monomers that are insoluble, which are subsequently polymerized to form fibrin. Normal platelet aggregation relies on FI as well in primary hemostasis. The presence or absence of abnormal circulating molecules determines whether an inherited FI disorder is classified as a full or partial quantitative deficiency

(afibrinogenemia or hypofibrinogenaemia, respectively), dysfibrinogenaemia or hypodysfibrinogenaemia [6].

In contrast to the often mild or nonexistent symptoms experienced by patients with hypofibrinogenaemia, dysfibrinogenaemia, or hypodysfibrinogenaemia, afibrinogenemic patients may exhibit a severe propensity for hemorrhage, which typically becomes apparent during neonatal period (in 85% of cases, this is seen as umbilical cord bleeding). Internal organ, genito-urinary tract, or central nervous system hemorrhage is another possible complication. Postpartum hemorrhage is common in women who do not receive preventive replacement medication, and women with a fibrinogenemia are more likely to undergo abortions in the first trimester. Thromboembolic consequences, which are likely caused by increased thrombin generation, have been observed in patients with a fibrinogenemia, frequently without replacement medication [7].

Cryoprecipitate, fresh-frozen plasma, and FI concentrate are the three products that are offered for replacement therapy. Because it is not infected with any viruses, this last treatment is preferred over cryoprecipitate and fresh-frozen plasma. While most people take FI as soon as they notice a bleed starting, there have been cases where taking it every 7–14 days for secondary prophylaxis (particularly after bleeding in the central nervous system) was effective [8,9].

Prothrombin deficiency

The 72 kDa single-chain glycoprotein known as prothrombin (FII) is produced in the liver and is one of the coagulation factors that rely on vitamin K. In order to acquire functional activity, it must undergo post-translational carboxylation. Approximately 21 kb of prothrombin is encoded by a gene on chromosome 11. Prothrombin consists of the following domains: Gla, kringle 1 and 2, and a serine protease domain. When factor Xa, factor vii, and calcium are present on platelet surfaces, the enzyme prothrombin is activated. Prothrombin cleavage releases an activating peptide, fragment 1+2 [10].

Among hereditary bleeding disorders, prothrombin deficiency is among the most uncommon, affecting an estimated 1 in 2 million individuals. Hypoprothrombinaemia, in which prothrombin and antigen levels are low, and dysprothrombinaemia, in which the protein is produced normally or almost so, are the two main phenotypes that can be distinguished from one another [5].

Extreme bleeding symptoms, such as gynaecological bleeding, intracerebral hemorrhages, gastrointestinal hemorrhages, and spontaneous haematomas and hemorrhages, are observed in homozygotes whose activity levels are less than 10% of normal. A total FII deficiency looks to be life-threatening. Clinical symptoms are typically not experienced by heterozygotes who have prothrombin deficiency [2].

Although antifibrinolytic drugs may be investigated for patients who have prothrombin coagulant activity above 20%, replacement therapy is typically not necessary in such cases. Only people who are homozygous, experience bleeding, or need to be adequately prophylactic before surgical procedures should undergo replacement treatment. Patients are treated with prothrombin complex concentrates since prothrombin concentrate is not available. Unlike fresh-frozen plasma, these

concentrates do not pose the danger of volume overload [11].

Factor V deficiency

FV is involved in both the prothrombinase complex's production of thrombin and the anticoagulant pathway's down-regulation of FVIII activity; both roles are important in blood clotting. A predisposition toward bleeding or thrombosis may thus be the outcome of FV deficiency [12]. Although most individuals with FV deficiency also have low antigen levels, about 25% of those patients have normal antigen levels but a defective protein, a condition known as type II deficiency. Located on chromosome 1, the FV gene is complex with 25 exons and big (80 kb). Although the majority of fibrinogen circulates in the bloodstream, around 20-25% is found within platelet α-granules, and it is produced by hepatocytes and megakaryocytes [13].

About half of all patients with FV deficiency will experience menorrhagia or epistaxis. Haemarthrosis and haematomas are other, less common symptoms that affect approximately 25% of patients. Intense hemorrhages affecting the brain or intestines are quite unusual. The fact that platelet FV may be compensating for the lack of a good correlation between bleeding tendency and FV level is noteworthy [14].

Since there is currently no FV concentrate on the market and neither cryoprecipitate nor prothrombin complex concentrates contain FV in sufficient quantities, the only way to replace FV is to administer fresh-frozen plasma, ideally inactivated by viruses [15].

Combined factor V and factor VIII deficiency

An autosomal recessive bleeding illness known as combined FV and FVIII deficiency occurs in approximately one instance per million people. It is clinically different from both FV deficiency and FVIII deficiency. It was not until 1998 that the molecular mechanism behind this connection was uncovered [16], When mutations in the LMAN1 gene—a 53 kDa type-1 transmembrane protein that chaperones the intracellular trafficking of both factors—were causally linked to the combined deficit, the gene was located on chromosome 18. A chromosomal 2 MCFD2 (multiple coagulation factor deficiency 2) gene abnormality was present in about 15% of afflicted families that did not have LMAN1 mutations. Encoding the MCFD2 protein, this gene is responsible for recruiting the cofactors LMAN1 and MCFD2 to the endoplasmic reticulum [17].

Low levels of coagulant activity and antigen, usually between 5 and 20%, are observed in combined FV and FVIII deficiency. The hemorrhagic tendency seen in persons with either of the individual coagulation problems does not seem to be amplified when both faults are present at the same time. After dental extractions, the most common and typically minor side effects include epistaxis, easy bruising, and bleeding. Some women who have been impacted have also reported menorrhagia and bleeding after giving birth. Few patients have reported bleeding in the gastrointestinal tract or central nervous system, and even fewer have experienced more serious symptoms including Haemarthrosis or bleeding from the umbilical cord. Rare are the cases of soft-tissue haematomas [18].

Currently, the only way to substitute FV is with fresh-frozen plasma, ideally with a virus-inactivated product, as there are no FV concentrates on the market. As an alternative, there are a plethora of goods that can be used in place of FVIII: In addition, during small bleeding episodes, the synthetic hormone desmopressin (DDAVP) can be administered to increase FVIII levels [19].

Factor VII deficiency

Another glycoprotein of around 50 kDa that depends on vitamin K is FVII. The F7 gene on chromosome 13 encodes it, and it is synthesized in the liver. An essential step in starting coagulation, FVII interacts with tissue factor. The levels of FVII activity (FVII:C) and antigen (FVII:Ag) in plasma are affected by a variety of environmental and genetic factors, including, but not limited to, F7 polymorphisms, gender, age, cholesterol, and triglyceride concentrations. The most prevalent autosomal recessive coagulation condition is FVII deficiency, with an incidence of 1 case per 500,000 people. Though some individuals may have normal or borderline low levels of FVII:Ag in contrast to reduced levels of FVII:C, the majority of afflicted individuals exhibit concurrently low levels of both proteins [20].

Plasma levels are not often well correlated with the intensity of symptoms in FVII insufficiency. Certain cases have not been able to halt bleeding despite significant hemostatic issues. Epistaxis and menorrhagia are the most prevalent symptoms, but dangerous bleeding rarely occurs [21]. Patients with FVII deficiency are at increased risk for thrombotic events, most often deep vein thrombosis, which can happen spontaneously or after surgery or replacement therapy (though it can happen in 3-4% of cases) [22].

Optimal treatment options for individuals suffering from FVII deficiency include recombinant FVIIa, which can be effective even at extremely low doses (10-20 µg/Kg), prothrombin complex concentrates, and FVII concentrates generated from plasma. This drug's main downside is its very short half-life. Repeated weekly administrations are required for consistent prophylaxis [23].

Factor X deficiency

Glycoprotein FX plays a crucial role in the coagulation cascade as the initial enzyme in the shared route of thrombin production. The 22 kilobase pair FX gene is located on chromosome 13, F10, and it is mostly responsible for liver protein synthesis. The severe (homozygous) form of FX deficiency is an autosomal recessive hereditary disorder that affects one person per million in the general population. Antigen levels can be normal or slightly below normal, coagulant activity levels can be low, or both can be present in FX deficiency, depending on the phenotypic [24].

Patients suffering with FX deficiency can experience bleeding at any age, but those with a more severe condition (FX:C <1%) Patients frequently suffer hemorrhage from the stump of the umbilical cord while they are infants. People who have significant impairments often have recurrent bleeding. Patients with FX deficiency most commonly describe epistaxis and menorrhagia, regardless of the severity of their bleeding symptoms [25].

The most common medical therapies for patients with FX insufficiency include plasma, concentrations of prothrombin complex, or a freeze-dried human coagulation

FIX/FX concentrate. Recently, an FX concentration produced from plasma with purity levels never seen before was established. Even though FX concentrations rise throughout pregnancy, women who have experienced significant FX insufficiency in the past and have had complications during their pregnancies, such as premature birth, abruptio placentae, or termination, may benefit from preventive replacement medication [26].

Factor XI deficiency

The liver is the primary site of production for FXI, a dimeric serine protease. The F11 gene, which is situated on chromosome 4, encodes it. It is 23 kb long. The functional activity of this plasma protein is reduced in FXI deficiency, typically accompanied by equally low levels of FXI:Ag. The presence of a defective version of the protein despite normal or borderline plasma FXI:Ag levels occurs less frequently. While the estimated frequency of severe FXI deficiency is approximately 1:1,000,000 in most groups, it is reportedly significantly higher in Ashkenazi Jews, with a heterozygosity prevalence of up to 8% [27].

Compared to hemophilia A or B, the bleeding symptoms of FXI deficiency are far harder to anticipate, even in the most extreme instances. The bleeding phenotype is associated with the damage site rather than the genotype. The risk of bleeding is significantly higher (49–67%) in circumstances when an injury occurs at a region with strong local fibrinolytic activity, such as the urogenital tract or the oral cavity following tooth extraction or tonsillectomy, compared to sites with lower local fibrinolytic activity (1.5–40%) [28].

Typically, patients suffering from a severe FXI deficit (FXI:C ≤1%) typically exhibit very modest symptoms, and the majority of their bleeding is caused by injuries. It appears that there is little difference in the clinical features of patients with low but detectable FXI levels and those with high levels, since both groups undergo minimal bleeding. This discovery was confirmed in a new group of non-Jewish Iranians who had mild to moderate FXI deficiency (FXI:C 6% to 30%) and severe or moderate deficiency (FXI:C <1% to 5%), mirroring what had been observed in Jewish persons before. Pregnancies in 70% of women with severe FXI deficit went successfully, even without prophylaxis. This is despite the fact that women with this deficiency tend to have heavy periods. Likewise, people who have alloantibodies that block FXI will not bleed naturally; any bleeding will occur only in the aftermath of trauma or surgery. The only way to reduce the risk of prolonged bleeding after surgery in patients treated with inhibitors utilizing fresh-frozen plasma or FXI concentrates is to identify the inhibitors prior to surgery [29].

The treatment is centered around ant fibrinolytic medicines, plasma-derived FXI concentrate, fresh-frozen plasma, and recombinant FVIIa. However, it is crucial to limit adverse events such as volume overload, allergic reactions, inhibitor development, thrombotic events (particularly with FXI concentrates), and so on. Due to the risk of excessive and prolonged bleeding following surgery, patients with severe FXI deficiency should undergo comprehensive pre-operative examination and have their procedures and post-operative periods carefully planned [30].

Factor XIII deficiency

The activation of the FXIII enzyme occurs last in the coagulation cascade. This transglutaminase strengthens clots by crosslinking α- and γ-fibrin chains, making them more resistant to fibrinolysis. Two FXIII-A subunits, which are catalytic, and two FXIII-B subunits, which are carrier subunits, make up the factor's heterotetramer in the plasma. In contrast to FXIII-B, which is synthesized in the liver, FXIII-A is generated by cells originating in the bone marrow. Chromosomes 1 and 6 contain the genes that code for this protein. Among the most uncommon recessively inherited clotting factor deficits, prothrombin and FXIII deficiency are extremely rare, affecting an estimated 1 in 2,000,000 individuals [31,32].

The FXIII-A subunit is typically found in very low plasma levels in inherited FXIII deficiency, as evaluated by functional activity or immunoreactive protein, while the FXIII-B subunit is present in reduced but always detectable amounts [32].

About 80% of patient's experience bleeding in the umbilical cord within the first few days of life, and up to 30% experience bleeding in the central nervous system. Severe bleeding tendencies and the rapid development of potentially fatal symptoms are hallmarks of patients with FXIII deficiency [33].

Approximately 80% of patients with FXIII-A deficiency experience severe bleeding, while 30% experience the early start of potentially fatal symptoms, such as bleeding from the umbilical cord and central nervous system, respectively. Intraperitoneal hemorrhage and miscarriage are common complaints among reproductive-aged women. Taken together, these signs and symptoms allow for prompt identification and preventative measures. Efficacious prophylaxis can be achieved with plasma levels of 2% to 5% FXIII, which are enough to stop serious bleeding. The in vivo half-life is 11 to 14 days, therefore replenishment is needed infrequently (1 month or longer). Crucially, the most current EN-RBD research showed that asymptomatic patients are exclusively those with FXIII:C > 30%. To avoid fetal loss, pregnant women who are lacking in FXIII-A should receive prophylactic FXIII infusions [34].

If FXIII concentrate is unavailable, other options include FFP and cryoprecipitate; the latter is better because it contains more FXIII.A new recombinant FXIII-A2 concentrate (rFXIII-A2) has been recently completed and showed that rFXIII is safe and effective in preventing bleeding in patients with congenital FXIII-A subunit deficiency; plasma-derived FXIII has been used for a while and is safe and effective. The use of rFXIII to treat FXIII-A deficiency has just been authorized in five countries: the US, Canada, the EU, and Australia [35].

While there have been a small number of recorded cases of inherited FXIII-B deficiency, the symptoms of bleeding caused by this deficiency seem to be less severe in patients with FXIII-B deficiency compared to those with FXIII-A deficiency [36].

CONCLUSIONS

Rare inherited bleeding disorders present with a wide range of symptoms, making diagnosis and therapy difficult. Rare inherited bleeding disorders are notoriously difficult to treat, so it's crucial that patients with a diagnosis be monitored closely at specialized hemophilia treatment centers. More research is required to improve the worldwide care for individuals

with rare inherited bleeding diseases. Also, pharmaceutical researchers need to do more to improve the accessibility and quality of factor concentrates for these diseases.

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