View Points

Factor V Deficiency: A Concise View

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ABSTRACT Coagulation factor V (FV; proaccelerin or labile factor), present in plasma and platelets, is an indispensable clotting factor. The generation of thrombin by the prothrombinase complex constitutes an essential step in hemostasis. In the prothrombinase complex, the activated form of coagulation factor V (FVa) is an essential co-factor to the enzyme activated factor X (FXa) and FXa is virtually ineffective in the absence of its cofactor. Surprisingly, however, severe FV deficiency is rarely fatal in humans. Although, several cases of life-threatening intracranial hemorrhage have been reported in FV-deficient newborns, many patients with undetectable FV levels experience only mild to moderate bleeding and do not require prophylaxis. While the reasons for this variable phenotypic expression are largely unknown, several observations from different laboratories indicate that platelets are crucial players in FV deficiency. FV deficiency can be caused by mutations in the FV gene or in genes encoding components of a putative cargo receptor that transports FV from endoplasmic reticulum to the Golgi complex. This review discusses and integrates these findings in the context of the biology of FV; clinical features of FV deficiency and treatment guidelines for severe symptomatic FV deficiency.

Key Words: Factor V Deficiency, symptomatic deficiency, treatment

Introduction

Coagulation factor V (FV), which is present in both plasma and platelets, is a versatile protein with both pro- and anticoagulant functions. It's essential role in the activation of prothrombin to thrombin and its interactions with several coagulation factors and inhibitors make it a central regulator of the coagulation process. The discovery of FV by the Norwegian Paul Owren in 1947 was based on the identification of a patient having severe bleeding tendency due to deficiency of a previously unknown coagulation factor (parahemophilia, Owren,s disease) [1]. FV deficiency states are associated with a bleeding tendency of variable severity, depending on the residual FV level. Among patients with undetectable FV levels, some present with life threatening intracranial hemorrhages at birth, whereas others born without any complications and experience only mild to moderate bleeding throughout their lives [2]. The comparatively mild bleeding diathesis observed in many patients with severe FV deficiency may be explained by the fact that < 1% FV is sufficient for minimal thrombin generation. However, there is no known explanation for the differences in bleeding phenotype between patients with equally undetectable FV levels.FV is synthesized primarily by the liver, and levels can decrease when the synthetic functions of live are impaired. Plasma FV circulates as a 330-KDa single-chain polypeptide that is the inactive procoagulant. Although most FV is present in plasma, approximately 20% of the circulating FV is found within platelet α-granules.

FV deficiency is inherited as an autosomal recessive disorder with an estimated frequency of 1 in 1 million. Beside the mutations in FV gene, deficiencies of FV can also arise due to acquired inhibitors to FV and defects that affect the storage and processing of FV. FV- specific inhibitors most often develop after exposure to preparations of bovine thrombin but have also been reported in patients who have underlying rheumatologic conditions, malignancies and who have been treated with antibiotics [4].

This review discusses the possible mechanisms that can ameliorate the hemorrhagic diathesis associated with severe FV deficiency. After a general introduction to the biology of FV and an overview of FV deficiency states, we focus on classical FV deficiency and discuss the possible role of platelet FV.

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Materials and methods

The PUBMED database was searched using the term "Factor V Deficiency". A total of 157 references were saved and read.

Epidemiology

No precise epidemiologic data exist for congenital FV deficiency. FV deficiency affects males and females with equal frequency [5]. It can affect all ages; the age of presentation indirectly varies with the severity of disease. Only 150 cases of congenital factor V deficiency have been reported worldwide since 1943.

Patho−physiology

Biosynthesis and structure of FV

FV is a large single chain glycoprotein of 330 kDa. Its plasma concentration is 20 nmol/L (0.007 g/L)[6]. FV is also present in the granules of platelets; this form account for 25% of the total FV content in human blood [7]. During coagulation, platelet FV is secreted as a result of platelet activation. Liver is believed to be the major site for biosynthesis of FV, where it is synthesized as a single-chain molecule, undergoing extensive post translational modifications before being secreted into blood. The evidence of platelet FV has not been established, but certain studies indicates that platelets or megakaryocytes can both endocytose and synthesize FV. Platelet FV is partially proteolysed and is stored bound to the protein multimerin in α-granules [3].

The FV gene (gene locus on chromosome 1q23) spans more than 80 kb and contains 25 exons. The isolated cDNA has a length of 6672 bp and encodes a preprotein of 2224 amino acids, including the 28-amino-acids residue long signal peptide [8]. FV has a mosaic-like structure, with a domain organization that is similar to that of factor VIII (FVIII), another essential coagulation cofactor protein [9]. The A domains of FV and FVIII together with those of ceruloplasmin have evolved from a common ancestor. Overall, the two coagulation factors (FV and FVIII) share 40% sequence identity in their A and C domains.

Role of plasma FV in coagulation:

Activated FV (FVa) is the cofactor in the pro-thrombinase complex that cleaves and activates prothrombin to thrombin [10]. This multi-component enzyme complex consists of FVa, calcium, phospholipids, and activated factor X (FXa). FVa increases the concentration of FXa at the membrane surface by acting as a receptor for FXa and allosterically alters the active site of FXa to optimize its ability to cleave prothrombin. By stabilizing the complex and increasing the rate at which FXa cleaves prothrombin, FVa enhances prothrombin activation by five orders of magnitude when compared with FXa alone [11].

As is the case with FVIII, FV activity is tightly regulated via site-specific proteolysis. Thrombin, and to a lesser extent FXa, are primarily responsible for FV activation via proteolytic cleavages at arginine residues in positions 709, 1018, and 1545. These cleavages release the B domain and create a dimeric molecule composed of a 105-kDa heavy chain that contains the A1 and A2 domains and a 71- to 74-kDa light chain that contains the A3, C1 and C2 domains. These two chains are held together by calcium and hydrophobic interactions. The heavy chain provides the contacts for both FXa and prothrombin, whereas the two C domains in the light chain are needed for the interaction of FVa with the phospholipid surface. The A3 domain in the light chain is involved in both FXa and phospholipids interactions. Taken together, these two FVa chains link FXa to the phospholipids surface formed by the platelet plug at the site of injury and enable FXa to efficiently bind and cleave prothrombin to generate thrombin.

Inactivation of FVa is mediated by activated protein C (APC), which cleaves FVa at arginine residues in positions 506, 306 and 679 and at lysine 994. The cleavage at Arg 506 reduces both the cofactor activity and its affinity for FXa, and the cleavage at Arg 306 completes the inactivation. Once cleaved at Arg 506, FVa is converted to FVac (FV anticoagulant), which interacts with APC and protein S to inactivate FVIIIa. Thus, APC not only turns off the Fva procoagulant activity but also converts it to an anticoagulant [11].

Special features of platelet FV

Although platelet FV originates from the plasma FV pool via endocytosis by bone marrow megakaryocytes, it has several structural and functional peculiarities that distinguish it from plasma FV. These properties are acquired by 'post-translational re-tailoring' of endocytosed plasma FV during its trafficking within the megakaryocytes. While plasma FV is a single-chain inactive procofactor, platelet FV is stored in a partially proteolysed form which already expresses considerable FXa-cofactor activity prior to exposure to FXa or thrombin. Further, platelet FVa is O-glycosylated at Thr402 and is resistant to phosphorylation of heavy chain at Ser692[12].

Platelet FV is activated by FXa 50-100 times more efficiently than by thrombin, whereas plasma FV is activated equally by both enzymes. Activation of platelet FV yields heavy (105 kDa) and light (72/74 kDa) chain fragments indistinguishable from those of

plasma FVa. Although APC cleaves platelet and plasma FVa at the same recognition sites, platelet FVa is proteolysed more slowly and cannot be completely inactivated by APC [13].

Platelet FV resides in the α-granules, where it is bound to the soluble protein multimerin 1 (MMRN 1) [14]. Upon platelet activation, platelet FV dissociates from MMRN 1 and is exposed on the platelet membrane as a fully activated cofactor, which promotes the assembly and activity of the prothrombinase complex at the platelet surface. Due to localized release of platelet FV at the site of injury, it has been estimated that the concentration of platelet FV with in a platelet-rich thrombus can exceed the plasma FV concentration > 100 times [15].

Storage in a partially activated form, targeted release, rapid activation by FXa and resistance to APC-mediated inactivation make platelet FVa a very effective FXa-cofactor, which can initiate prothrombinase activity before plasma FV is activated and sustain this activity long after plasma FVa has been inactivated.

Levels associated with severity of bleeding

The FV activity level has limited correlation with the severity of bleeding. Overall, patients with lower levels are more likely to have bleeding episodes than those with higher levels. Patients who come to medical attention are typically symptomatic homozygous or compound heterozygous with FV activity less than 5 % [16]. However, the severity of the clinical phenotype cannot be easily predicted by the activity level. Patients with identical mutations or activity levels can vary greatly in their bleeding symptoms [16].

Classification of FV deficiency states

FV deficiency can be categorized as either congenital or acquired.

1.Congenital Deficiencies:

The congenital deficiencies arise from either mutation in FV gene itself or in genes that affect the processing or storage of FV. Mutation in FV gene itself can result in either a quantitative (typ1) or a qualitative (type II) defect. Mutations in LMAN1 or MCFD2 lead to combined FV and FVIII deficiency.

2.Acquired Deficiencies:

Although pathological conditions such as severe liver disease or disseminated intravascular coagulation (DIC) can cause a decrease in FV levels, the most common form of acquired FV deficiency is associated with the development of FV inhibitors, i.e. antibodies that bind to FV and promote its degradation and/or block its activity. Acquired FV inhibitors may cause various degrees of FV deficiency. The clinical presentation ranges from complete absence of symptoms to life-threatening hemorrhages. Acute bleeding episodes are treated with fresh frozen plasma and/or platelet concentrates, whereas the follow-up therapy (immunosuppression, injection of intravenous immunoglobulins, plasmapheresis or plasma adsorption) is aimed at lowering the antibody titer. In most cases, the FV inhibitor is transient and disappears within a few months.

Factor V inhibitors only rarely develop spontaneously. Mostly, they are triggered by the exposure to topical bovine thrombin preparations (containing traces of bovine FVa) during surgical procedures, or by the use of certain antibiotics. However, the most important determinants of clinical outcomes are the specific characteristics of the antibody, such as (i) the antibody titer (ii) whether or not the antibody has access to platelet FV (iii) the FV epitope recognized by the antibody. In particular, the antibodies directed against the C2 domain of FV (which mediates the binding of FV (a) to phospholipids membranes) often results in clinical bleeding[17].

3.Platelet FV deficiency

Que'bec platelet disorder (QPD) is an inherited bleeding disorder segregating as an autosomal dominant trait [18]. Affected individuals present with a variety of bleeding symptoms, ranging from easy bruising to joint bleeds, their most typical features being delayed-onset bleeding after hemostatic challenges. Many studies have revealed that not only FV, but most a-granule proteins are decreased/degraded in platelets from QPD patients [19]. This is now known to be due to >100-fold increased expression of the urokinase-type plasminogen activator (u-PA) in QPD megakarocytes, leading to plasmin generation within the platelets and proteolysis of α-granular proteins [20]. In line with these findings, accelerated fibrinolysis due to massive release of platelet-derived u-PA at the site of injuries is currently considered the primary cause of the characteristic delayed-onset bleeding observed in QPD patients. Linkage analysis has recently shown that QPD is linked to the u-PA structural gene (PLAU) on chromosome 10, although the causative mutation has not been identified yet [19].

Factor V New York is a bleeding disorder characterized by a mild deficiency of platelet FV antigen and activity in the presence of normal levels of plasma FV. In contrast to QPD, FV New York is not a storage pool deficiency, as other α-granular proteins are normal. The patients with this disorder usually present with moderate bleeding diathesis, especially after surgical challenge. The molecular defect underlying FV New York is currently

unknown[21).

Clinical Manifestations

Approximately 200 patients with FV deficiency have been described in the literature. Unlike patients with hemophilia A and B, FV deficient patients are more likely to have skin and mucocutaneous bleeding rather than hemarthrosis.

Relation to level of deficiency:

In the more severely affected subgroup of the North American registry, 44% of the bleeding episodes were in skin and mucosa, 23% in joint and muscle, 19% in the genitourinary tract, 6% in the gastrointestinal tract, and 8% in the CNS. Bleeding episodes in the mildly affected subgroup consisted of 62% skin and mucous membrane bleeding and 19% each of musculoskeletal and genitourinary bleeding events [22].

Timing of presentation:

Most cases of FV deficiency manifest themselves at birth or in early childhood, but some remain virtually asymptomatic until later in life and may be discovered incidentally during routine coagulation screening. Heterozygous are usually asymptomatic or experience only mild bleeding whereas homozygote's and compound zygotes show a mild to moderate bleeding diathesis depending on residual FV level. This correlation between FV level and bleeding phenotypes is lost in the low FV range (< 5%), where patients with equal FV levels may show very different clinical phenotypes.

The most common symptoms associated with FV deficiency are bleeding from mucous membranes e.g. epistaxis, menorrhagia in females and post-traumatic bleeding following surgery or delivery, which occur in approximately half of all FV-deficient individuals. Hemarthrosis and muscle hematomas are present only in a small number of patients and severe bleeding manifestations like intracranial or gastro-intestinal hemorrhages are rare and confined only to patients with undetectable FV levels. Several cases of severe FV deficiency presenting with life-threatening neonatal/perinatal intracranial hematomas have also been reported [23].

Diagnosis

Typically, FV deficiency is suspected in a patient with bleeding episodes, positive family history or on routine coagulation tests [22]. In FV deficiency, prothrombin time and partial thromboplastin are prolonged, but conclusive diagnosis requires the measurement of plasma FV antigen and/or activity levels. If FV levels are reduced, additional testing is needed to exclude combined FV/FVIII deficiency.

The clinical history is also important to distinguish congenital FV deficiency from an acquired inhibitor to FV. Inhibitors are most often associated with surgical procedures in which topical bovine thrombin has been used. If an inhibitor is suspected, its presence should be confirmed with a mixing study and inhibitor titer determined with a Bethesda assay.

Prenatally obtained FV levels need to be interpreted with caution, as FV levels appear to be developmentally regulated. At 19~32 weeks of gestation, the mean FV level is 32.1%, whereas it is 48.9% at 30~38 weeks and 89.9% at term [24]. However, prenatal molecular diagnosis is possible in theory if the mutations in both parents are known and facilities are available for sequencing the fetal DNA.

Management

In the absence of FV-specific concentrates, fresh frozen plasma (FFP) is the primary therapeutic option for symptomatic FV deficiency. For less severe bleeding, antifibrinolytic agents such as aminocaproic acid may be sufficient [22]. Patients with menorrhagia may also benefit from hormonal therapy. In contrast to severe hemophiliacs, patients with severe FV deficiency do not need routine prophylaxis.

For procedures and acute hemorrhage, the goal therapy is to maintain FV level above 20%. The half life of FV is 12~36 hours, so daily infusions of (15~20) ml/kg of FFP are sufficient. But the dosing should be adjusted empirically to achieve homeostasis. Besides concerns of potential allergic reactions and infection, treatment with FFP has the additional risk of volume overload. Plasma exchange has been successfully used to circumvent this complication.

Rarely, FV-deficient patients have developed inhibitors to FV after receiving FFP. For such patients, activated prothrombin complex concentrate (FEIBA) and rFVIIa concentrate are the options. The latter has been reported to be effective in patients with severe FV deficiency. Platelet transfusion may provide a source of FV that is more resistant to inhibition by circulating antibodies.

Conclusion

The complex patho-physiology of congenital FV deficiency is just starting to be unrevealed. Given that the FV level required for minimal homeostasis is extremely low, subtle difference

in plasma and/or platelet FV levels may be crucial to clinical outcome. Residual platelet FV might be responsible for the vast differences in bleeding phenotypes observed among patients with equally undetectable plasma FV levels. Although, while several studies support the role of platelet FV in maintaining adequate homeostasis, available data on platelet FV in patients with severe congenital FV deficiency are too scanty to allow definite conclusions. Overall, the prognosis of most FV-deficient patients is good, but still severe cases like intracranial hemorrhage have been reported.

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