

Combined Factor V and VIII Deficiency

H. Mansouritorghabeh

Abstract

This review summarizes current data on the pathomechanisms and new genetic findings of combined factor V and VIII deficiency (CF5F8D). Congenital haemorrhagic disorders characterized by deficiency of two clotting factors comprise an interesting group. Among dual coagulation disorders, CF5F8D is the most common type. For the first time combined factor V and VIII deficiency (F5F8D) was reported by *Oeri et al* in 1954. That is distinct from the coinheritance of both FV deficiency (parahaemophilia) and FVIII deficiency (haemophilia A) that has been reported in four families. Individuals who present with this phenotype have between 5 and 30% of normal plasma levels of FV and FVIII antigen and activity, whereas the level of other plasma proteins are not altered. Total numbers of affected individuals are less than 150 cases all over the world. At first it was assumed that deficiency of protein C inhibitor was a responsible cause, but further investigations revealed that it was due to mutations called ERGIC-53 and LMAN-1.

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Definition and demography of CF5F8D

Dr. Oeri et al. made the first report on CF5F8D, when studied two young brothers, who were born of a consanguineous marriage with haemorrhagic symptoms.¹ The combined deficiency is diagnosed when factor V coagulant activity is <40% and factor VIII coagulant activity is <45%. This phenotype of disorder has identical frequency in both males and females.² It can be differentiated by a mild to moderate haemorrhagic presentation.³ In concern to differential diagnosis of CF5F8D from co-inheritance factor V (parahaemophilia) and factor VIII deficiency (haemophilia A) following points may be advantageous:

1. Co-inheritance of factor V & VIII deficiency is a completely rare coagulation disorder and only four cases have been reported so far but CF5F8D is more common and most of reported cases had history of consanguinity mating in their parents.
2. The affected individuals with CF5F8D have prolonged partials thromboplastin time (PTT) and also a moderately prolonged prothrombin time (PT).
3. They respond well to coagulation products such as cryoprecipitate and FFP that have both factors V & VIII, despite not complete response to factor VIII concentrates.
4. Molecular approach can definitely differentiate these coagulation disorders that have complete diverse mutations.

Immunology Laboratory,
Chaem Hospital,
Mashhad University of Medical Sciences,
Mashhad, Iran.

Correspondence:

Hassan Mansouritorghabeh Msc,
Immunology Lab,
Ghaem Hospital,
Zip Code: 91766-99199,
Mashhad, Iran.
Tel: +98 511 8012761
Fax: +98 512 42225157
Email: Mansouritorghabe@mums.ac.ir

The frequency of CF5F8D was described in Israel with an estimated prevalence of 1:100000 among non-Ashkenazi Jews.⁴ Inherited combined factor V and VIII deficiency is a rare occurrence. A total of 106 recognized cases were reported according to a literature review in 1998,⁵ and three additional families by the end of 2002,^{6,7} after this time according to our current review of literature there are three other reports with 2, 19 and 1 patients from Italy, Iran and Thailand.⁶⁻⁸ In our review of literatures total number of affected individuals until end of May 2006, reach to 138 persons.

Most of patients are from Mediterranean region including area which consanguineous marriage is common, such as Israel,⁴ Iran,^{5,7} and Italy.⁹ Additional families have been reported from India,^{10,11} Japan,¹² North America and Europe.⁹

Also in our review of literatures from Iran, it was revealed total reported cases with CF5F8D included 77 cases (table 1). As total reported cases in Iran reach to about 77 persons, regarding total reported cases worldwide (about 138), we can conclude in a rude estimation that about half of reported cases related to Iran. This is due to high consanguinity marriage rate in Iran. However, it should be remembered that, there may be more undiagnosed affected individuals in other Iranian provinces.

Table 1: The total reported individuals with CF5F8D from Iran until May 2006.

Location in Iran	Number of patients	Family	Reference
Centre (Shiraz)	22	17	Shahriari ¹³
Center (Shiraz)	1	1	Karimi ¹⁴
North-west (Azarbayejan)	2	?	Ziaei ¹⁵
Center (Tehran)	27	16	Peyvandi ⁵
North-eastern (Khorasan)	25	9	Mansouritorghabeh ^{7,16}
Total	77	53	

?= not reported.

Haemorrhagic symptoms and treatments

The treatments of bleeding episodes are dependant on the nature of the bleed and levels of factor V and factor VIII in plasma of affected individuals. According to reported data mucocutaneous bleeding such as epistaxis and post-surgical bleeding such as after circumcision were the most frequent clinical manifestations.^{5,7} Spontaneous bleeding can be treated with both FFP (as a source of FV) and FVIII concentrates. Surgical procedures should be covered with factor VIII concentrates adminis-

trated each 12 hour to maintain factor VIII level above 50 IU/dL and each 12 hour FFP to achieve minimum level of FV of 25 IU/dL until wound healing was established.¹⁷ This bleeding disorder has been treated with replacement therapy with plasma infusion (or plasma exchange) as a source of FV and FVIII, DDAVP or FVIII concentrate depending on the severity of the haemorrhage or of the invasive procedure.^{6,18} The use of desmopressin was shown to be effective in an 8-year-old boy who underwent circumcision.^{19,20} Also Baunduer et al have reported successful transurethral prostatectomy with use of FFP and desmopressin.²¹ There is also a report on successful dental extraction in an individual with CF5F8D using local haemostatic treatment and the transfusion of fresh plasma.²²

Coagulation factors V and VIII

Coagulation factors V and VIII are plasma glycoproteins of approximately 280 and 330 KDa, respectively, that function as essential cofactors in the blood coagulation cascade. Factor V is synthesized primarily in megakaryocytes and hepatocytes and is found in the α -granules of platelets, but factor VIII is most likely synthesized in the hepatocytes and reticuloendothelial cells.^{22,23} They are both synthesized in liver as single chain polypeptides having the identical domain structure in order of A1-A2-B-A3-C1-C2 (figure 1).² The A domains are nearly similar to ceruloplasmin and the C domains are similar with discoidin, a slime sort of protein; the B domains are dissimilar. Both proteins hold free cysteine residues.³ Although their respective A and C domains exhibit 40% amino acid sequence identity and provide important roles in coagulation cascade.²³

The plasma levels of factor V and factor VIII in individuals with combined factor V and VIII deficiency are between 5 and 30% both for antigen and activities. Although there are dual coagulation deficiency in this phenotype of disorder, but individuals with CF5F8D show less haemorrhage in comparison with severe haemophilia A.

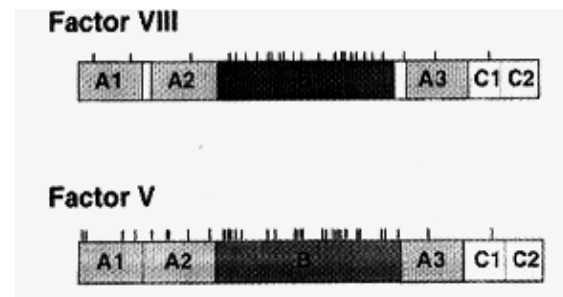


Figure 1: Domains structure of factors V and VIII. Domain homology is indicated by similar shading. Vertical dashes indicate consensus sites for N-linked glycosylation.²⁴

Inheritance

The report of several cases with CF5F8D in 1950s and 1960s suggested that the common occurrence of factor V and factor VIII deficiencies was not a mere coincidence of parahaemophilia and hemophilia A. This was further supported by the observation that in five of the eight families reported up to 1969, the affected individuals were descendents of parental consanguinity.²³

How could one explain this mechanism of inheritance with one gene on the X-chromosome, and another gene located on an autosome? This enigma had attracted the interest of investigators to the pathogenesis of disorder in the subsequent years.^{23,25} However pattern of this phenotype is autosomal recessive, which is manifested in homozygotes by a severe bleeding tendency highlighted by substantially reduced factor V and factor VIII levels, and in heterozygotes by partially deficient or normal factor levels.

Pathogenesis

Two types of coat proteins on vesicles are known to participate in the transport between the endoplasmic reticulum (ER) and the Golgi complex: coat proteins (COP) I and COP II. COP II acts earlier in the pathway apparently driving the initial budding of vesicles from the ER (figure 2). The ERGIC-53 is the site of segregation of secretory proteins for anterograde transport, via packaging into COPII-coated transport vesicles. The majority of individuals with CF5F8D have null mutations in the protein called Endoplasmic Reticulum Golgi Intermediate Compartment ERGIC-53. The existence of ERGIC-53 to facilitate selective glycoprotein transport provides the first example of a chaperone that mediate ER to Golgi transport in higher eukaryotic cells.

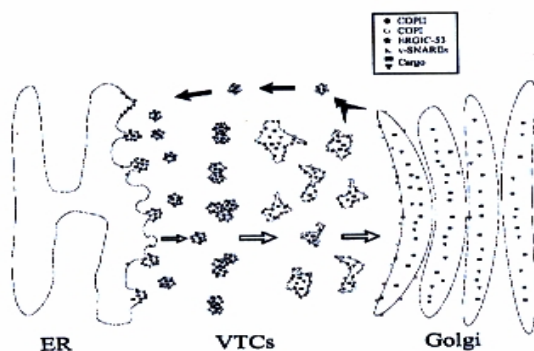


Figure 2: ER to Golgi transport. This drawing depicts events involved in both anterograde and retrograde trafficking, between the ER and the Golgi. COPII-coated vesicles, containing v-SNAREs, ERGIC-53, and cargo proteins, bud off from the ER (unblackened arrows). Then vesicles fuse to form components of the ERGIC, and ERGIC clusters move in a microtubule-dependent manner toward the Golgi and finally buds from both ERGIC and Golgi apparatus (blackened arrows).²⁴

Genetics

One of the most interesting and prime model was based on finding of survey on four separate individuals with CF5F8D. The primary investigation showed that there was no detectable protein C inhibitor (PCI) in the plasma of affected ones. Normally protein C, a protease zymogene, after activation during cleaving by thrombin and inactive and destroy activated forms of both coagulation factors V and VIII in blood. So current physiologic anticoagulant can limit coagulation cascade to injury site and stop expansion of it to healthy parts of vessels. The PCI set the activity and level of PC by destroying extra amount of PC. As a result lack of PCI will terminate to additional amount of PC, which in turn will terminate to unopposed decrease of both factors V and VIII in blood.²⁵ It was in 1980 that *Marler* and *Griffen* reported an apparent deficiency of protein C inhibitor as the underlying mechanism for this disorder.²⁶ Subsequent researches failed to confirm it,^{27,28} because the clearance of administrated coagulation factors V and VIII was revealed to be normal, and the endogenous factor VIII secreted and increased by a dose of 1-desamino-8-D-arginine-vasopressin (DDAVP). Further observations showed that coagulation factor VIII had normal half-life in blood; thus, accelerated destruction of factors V and VIII wasn't the trouble. Other affected persons also showed normal PCI levels, "A beautiful hypothesis that killed by an ugly fact". After exact evaluation of the original patients' samples, normal PCI level revealed and the primary finding of PCI deficiency was contributed to susceptibility and weakness of PCI upon repeated freezing and thawing of plasma samples.

The cause of this disorder remained a mystery until a direct genetic approach became possible, as a result of the human genome project. For first time *Seligsohn et al* could solve this mysterious dilemma and question by their pioneer investigation using genetic approach.²⁹ They evaluate these affected families with CF5F8D carefully and concomitant with other scientific teams. They could evaluate current pedigree using a genetic method entitled homozygosity mapping and could address responsible gene in most of affected members to be located on long arm of chromosome 9. This finding subsequently confirmed by another group.³⁰ Further genetic works on the disorder (F5F8D; OMIM accession number 227300) had identified a genetic mutation that causes defects in a protein called ERGIC-53 also known as Lectine Mannose Binding Protein I (LMAN-1) that encoded by a gene on chromosome 18q21. ERGIC-53 participates in

cellular events that ensure that secretor and membrane proteins undergo proper folding, oligomerization, and maturation before exit from the ER.³¹ Detection underlying cause of CF5F8D in mutations located in LMAN1 recommended current gene takes part in transportations of coagulation factors V and VIII between ER and Golgi apparatus which apparently prevented a cell from secreting factor V and factor VIII.^{16,32} To date, 17 different mutations have been identified. All but one of the mutations are either non-sense or frameshift alleles whose truncated proteins products would be predicted to lack of normal LMAN1 function.³³ But about 30% of the F5F8D individuals had normal levels of LMAN-1, so this mutation alone couldn't account for all of the disease.^{34,35}

What the researchers found is that a mutation in a second gene, called Multiple Coagulation Factor Deficiency 2 (MCFD2), can result in the same disease state. The researchers proposed that these two proteins, LMAN1 and MCFD2, bind together to form a transporter which is specifically tailored to carry the two blood clotting factors from the cell's endoplasmic reticulum to Golgi body, in other word MCFD2 acts as a cofactor for LMAN-1.^{36,37} MCFD2 interacts with LMAN1 in a calcium binding manner. Missense mutations within the second MCFD2 disrupt this interaction. A mutation in the gene that makes either of the two proteins will results in a malformed transporter, and thus the inability to secrete factor V and factor VIII.³⁸

There were still families who have bleeding disorder, but were not found to have mutations in either LMAN-1 or MCFD2 genes,^{39,40} but recent study by Zhang et al. showed mutations in LMAN-1 and MCFD2 may account for all cases of F5F8D.⁴¹

It seems that these two proteins shape a compound that acts as a cargo-receptor for special facilitated transport of a particular series of proteins, including coagulation factors V and VIII. This striking model shows how findings resulted from patho-physiology of a human disorder can offer new insight and imminent into basic biologic burdens. On top, current molecular data provide a new biological route and pathway that emphasis on haemostatic balance and show a probable source of modifier gene integrated in haemostatic disorder. Also on the other hand one could see in his mind's eye that polymorphic variation within components of current system could alter plasma levels of coagulation factors V and VIII and thereby change risk of haemorrhage and thrombosis. This hypothesis remained to be addressed in future.⁴²

Perspective

The CF5F8D is an informative pattern of haemorrhagic phenotype in which the responsible genes for coagulation factors V and VIII are normal in structure and function, but defects in proteins that have main roles in post-translational processes cause deficiency of coagulation factors.

Finally identification of the LMAN1 and MCFD2 genes may also provide a target for the development of novel anticoagulant therapies in the future, as well as potential tools for more efficient production of recombinant factors V and VIII.²⁹

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