Factor VII Deficiency

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ABSTRACT

The complex formed between the procoagulant serine protease activated factor VII (FVII) and the membrane protein tissue factor, exposed on the vascular lumen upon injury, triggers the initiation of blood clotting. This review describes the clinical picture of FVII deficiency and provides information on diagnosis and management of the disease. FVII deficiency, the most common among the rare congenital coagulation disorders, is transmitted with autosomal recessive inheritance. Clinical phenotypes range from asymptomatic condition, even in homozygotes, to severe disease characterized by life-threatening and disabling symptoms (central nervous system and gastrointestinal bleeding and hemarthrosis), with early age of presentation and the need for prophylaxis. In females, menorrhagia is prevalent and affects two thirds of the patients of fertile age. Although FVII gene mutations are extremely heterogeneous, several recurrent mutations have been reported, a few of them relatively frequent. The study of genotype-phenotype relationships indicates that modifier (environmental and/or inherited) components modulate expressivity of FVII deficiency, as reflected by patients with identical FVII mutations and discordant clinical phenotypes. Several treatment options are available for FVII deficiency: the most effective are plasma-derived FVII concentrates and recombinant activated FVII (rFVIIa). Treatment-related side effects are rare.

KEYWORDS: FVII deficiency, F7 database, F7 genotypes, FVII bleeding phenotype, replacement therapy

The complex formed between the procoagulant serine protease activated factor VII (FVIIa), a plasma vitamin K–dependent serine protease, and the integral membrane protein tissue factor (TF) exposed on the vascular lumen upon injury triggers the initiation of blood clotting. The action of the FVIIa-TF complex generates a burst of activated factors IX (FIXa) and X (FXa), which ultimately leads to formation of a stable fibrin clot.1–3

Inherited FVII deficiency is the most common among the rare congenital coagulation disorders and is characterized by autosomal recessive inheritance. Clinical heterogeneity is a feature of this hemorrhagic disorder, which ranges in severity from lethal to mild or even asymptomatic forms.4–6 FVII deficiency is not believed to be associated with complete absence of functional FVII, as also reflected on studies on knockout mice,7 which suggest that a complete lack of FVII is incompatible with life. The molecular genetics, FVII structure/function analysis, and pathophysiology of FVII deficiency have been extensively investigated.8–14

Comprehensive studies based on clinical issues and involving a very large patient population have greatly contributed to our knowledge of disease presentation and diagnosis.6 The relationship between gender and bleeding tendency has been also investigated. It is known

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that FVII levels are clearly modulated by \textit{FVII} gene polymorphisms\textsuperscript{15,16} and databases of mutations are available for comparison.\textsuperscript{8}

### Clinical Manifestations

The most frequent symptoms (Table 1) indicate that the disease is mild in the majority of cases, mimicking the clinical picture of a platelet disorder. However, severe to very severe cases are not infrequent, characterized by disease presentation symptoms, by hemarthrosis, muscle hematomas, or even central nervous system (CNS) and gastrointestinal (GI) bleeding. Postoperative bleeding may also occur, and clotting tests may not be helpful in predicting the inherent bleeding risk.\textsuperscript{17} In females, menorrhagia is prevalent\textsuperscript{6} (Table 2) as per the other autosomal inherited congenital bleeding disorders.\textsuperscript{18,19}

### Factor VII Deficiency and Thrombosis

Surprisingly, thrombotic episodes (particularly deep vein thrombosis), have been reported in 3 to 4\% of patients with FVII deficiency, particularly in the presence of surgery and replacement treatments but "spontaneous" thrombosis may occur as well.\textsuperscript{20,21}

### FVII Deficiency in Women

As in the other autosomal inherited congenital bleeding disorders, menorrhagia is a frequent type of bleeding in FVII deficiency (Table 2),\textsuperscript{6,17} accounting for a prevalence of two thirds of women aged 10 to 50 years, with a peak prevalence in teenagers. Menorrhagia may be associated with other gynecologic (i.e., hemoperitoneum related to ovarian cysts, metrorrhagia due to uterine fibromatosis) or obstetric (postpartum hemorrhage) problems.

In general, women with FVII deficiency do not display a bleeding tendency different from that observed in males (Table 2). In addition, the analysis of the bleeding-free survival is characterized by very similar median survival and curve shapes (data not shown).

### Laboratory Assays

#### Phenotype Analysis

The diagnosis of FVII deficiency is typically simple, relying on the discordance between the prolonged prothrombin time (PT) and the normality of the activated partial thromboplastin time (APTT) tests. Prolongation of the international normalized ratio (INR) may be from moderate (1.5 to 1.8) to high (>2.0), depending on the plasma FVII coagulant (FVII:C) levels.

The FVII:C assay is an important test for the diagnosis, but attention is required for the evaluation of levels around or below 1\%, due to the potential presence of traces of FVII in deficient plasmas.\textsuperscript{26} A carrier detection approach based on FVII activity and antigen determinations has also been proposed.\textsuperscript{27}

Activated FVII (FVIIa) deficiency should be considered the crucial biochemical event in FVII deficiency, because this weak enzyme is the real trigger of blood coagulation. The assessment of FVIIa deficiency, which can be achieved by clotting-based assays (available
from Stago, Asnières sur Seine, France) or enzyme-linked immunosorbent assay (ELISA), is not performed routinely in this bleeding disorder. Normal levels of FVIIa range from 5 to 15 ng/mL (i.e., 1 to 3% of the inactive zymogen form). It is worth noting that the PT assay performed with recombinant-thrombin time (TF) is extremely sensitive to tiny amounts of FVIIa. Factor VII antigen can be quantitatively assayed with polyclonal antibodies to FVII by an ELISA assay (available from Stago)\(^2\) or by using an amidolytic method.\(^4\) An antigen assay is useful to identify the dysfunctional forms of FVII deficiency, characterized by a discrepancy between clotting assay values and antigen levels.

The generation of FXa in plasma, or using recombinant molecules, has been estimated using the FXa fluorogenic substrate MeSO2-D-CHA-Gly-Arg-AMCAcOH (American Diagnostica, Stamford, CT, USA).\(^2\)

Thrombin generation has also been used to evaluate features of FVII-deficient patients. A small amount of FVII is able to guarantee an appreciable thrombin generation.\(^2\)

**Genotype Analysis**

The FVII gene (F7) is located on chromosome 13q34,\(^3\) 2.8 kb upstream of the FX gene (FX), and contains nine exons (Fig. 1) encoding the FVII protein circulating in plasma as a 406-amino-acid single chain (50 kDa).\(^3\) FVII proteolytic activation generates two chains: the light chain, which contains the gamma-carboxylglutamic acid (Gla) domain and two epidermal growth factor–like
Human FVII cDNA. The processing of altered FVII expression vectors after site-directed mutagenesis of the obtained in cultured eukaryotic cells transfected with the have been investigated by recombinant FVII molecules. Moreover, the expression of mutations detected in FVII-deficient patients has been associated with consanguinity caused by genetic components in the modulation of both the function of the clotting process and the penetrance of FVII deficiency.

Phenotype-Genotype Correlation

Patients homozygous for the same mutation do not always belong to the same class of severity (Table 3), indicating phenotypic heterogeneity in the presence of identical FVII gene mutations. These observations, as well as the report of several symptomatic heterozygotes, suggests a role for environmental factors and/or other genetic components in the modulation of both the function of the clotting process and the penetrance of FVII deficiency.

PROBLEMS WITH LABORATORY DIAGNOSIS

The diagnostic efficiency of the FVII:C assay is highly dependent on the thromboplastin sensitivity (i.e., reagent ISI, or international sensitivity index). In general, recombinant thromboplastins structurally identical to the human TF are the most sensitive for the detecting the defect (give the longest clotting times), and should therefore be used to assay FVII levels when there is the suspicion of such deficiency. It is important to note, however, that the FVII:C assay measures both the zymogen (FVII) and the active enzyme (FVIIa).

The quality of deficient plasmas is also important for accurate measurement of very low levels of FVII. In general, small amounts of residual FVII are present in these reactants, which makes it difficult to assay residual FV in patients with very severe defects (i.e., those in whom we expect levels consistently lower than 1%). Accordingly, levels of FVII around or below 1% are often questionable. More sensitive activity methods are those based on thrombin generation assays, especially when fluorogenic substrates for the detection of thrombin are used; these methods are made more sensitive by using highly diluted TF to trigger the reaction.

Several FVIIa assays have recently become available using one of two assay methods. One is “clot-based” (the TF is of bovine origin) and the other utilizes ELISA.
technology. The usefulness of these assays is questionable in FVII deficiency, whereas assessment of FVIIa by antigen assay would help to identify the dysfunctional variants. It is also important to mention that the clotting FVIIa assay should preferably be performed at specialized centers due to several technical challenges.

Monitoring of replacement treatment in FVII deficiency is currently best achieved using a FVII activity assay, which is, as outlined previously, sensitive to both the zymogen and FVIIa, although extremely sensitive to the latter. The FVIIa assay is only effective for monitoring FVIIa. For routine monitoring at the bedside, the PT-INR may be sufficient, because its normalization roughly correlates with the hemostatic levels. In fact, levels close to 50% of the reference plasma FVII content are associated with the lowest "normal" INR values (1.15 to 1.18).

PREGNATAL DIAGNOSIS
Prenatal diagnosis in severe FVII deficiency has been successfully performed both by coagulation assays and by molecular genetic methods, although the former method is technically challenging. The presence of repeated regions, and of polymorphic variation of repeats within the FVII genes, requires careful design of PCR primers to detect gene rearrangements.

TREATMENT
Patients with FVII deficiency can be offered several therapeutic options (Table 4), which may result in a very effective correction of the disease. Fresh-frozen plasma (FFP) is still used in developing countries, the most important drawback being the blood volume overload and a relatively high risk of transmitting blood-borne viruses. Plasma-derived FVII (pdFVII) concentrates are essentially prothrombin complex concentrates (PCCs) with a higher content of FVII but are effective for any therapeutic requirement. Together with the regular PCCs, pdFVII concentrates were reported to be associated with posttreatment thrombosis.

Recombinant FVIIa is to be considered the optimal replacement therapy as FVIIa is the enzyme to be replaced; it can be used at a low dose (15 to 30 μg/kg body weight) compared with dosing in hemophilic patients with inhibitors.

Prophylaxis has been a debated issue in FVII deficiency, especially because of the very short half-life of infused FVII in the blood, and especially in childhood where prophylaxis is of particular importance. Recent anecdotal observations suggest that secondary prophylaxis can be performed with FFP (very low concentration of FVII) infusions. Moreover, ex vivo studies showed that infused recombinant FVIIa disappears quickly from the circulation but persists extravascularly, bound to pericytes. These observations would support the feasibility of prophylaxis in FVII deficiency, but larger trials are needed to assess the optimal schedule. At any rate, the main target for prophylaxis are the newborns who have had early and severe (CNS, GI) bleeds.

The same uncertainty holds for prophylaxis courses for the prevention of bleeding and after surgical interventions: a wide array of dosages and schedules has been employed. In some cases, surgery has been performed without any replacement therapy, namely in patients with a poor bleeding history, but these patients were not homogenous in terms of genotype or cloting phenotype. For both bleeding prevention and treatment of spontaneous bleeds, pdFVII concentrates and recombinant FVIIa seem to be equally effective, although no formal comparative studies have been published.
single, standard dose capable of inducing hemostatic levels, it ranges from 15 to 25 μg/kg body weight for recombinant FVIIa and from 10 to 30 IU/kg body weight for the pdFVII preparations (STER registry, unpublished data). Due to the short half-life, more than one daily administration should be given, if possible. Both preparations are suitable for home care.

With regard to the kinetics of infused FVII, scant data are available, which, nonetheless, confirms the very short half-life, especially in children.41,42

The complications of treatment, excluding transmission of blood-borne viruses (very rare today), are confined to the occurrence of thrombosis20,21 (as a rare complication of replacement therapy or sometimes spontaneous), or the even rarer appearance of inhibitors to FVII (with a probable prevalence of ~1% of the treated patients).43

### Treatment in Women: Pregnancy, Delivery, and Menorrhagia

As outlined before, menorrhagia is prevalent in women with a severe deficiency, especially after menarche. This is almost invariably associated with iron deficiency and iron-deficiency anemia. The occurrence of frequent menorrhagic menses may require treatment or even an ad hoc “prophylaxis” consisting of replacement therapy (as previously outlined) during the first days of the menses. Pregnancy itself does not require special precautions, whereas delivery should occur under the coverage of a short-term replacement therapy.43

### REFERENCES

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