Inherited factor VII deficiency

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Abstract
Factor VII (FVII) deficiency is a rare hereditary hemorrhagic disease caused by the diminution or absence of this coagulation factor. It is transmitted by autosomal recessive inheritance. Only homozygotes or compound heterozygotes (that is, with two different mutations) develop a hemorrhagic syndrome; heterozygotes are asymptomatic. The clinical expression of this disorder is highly variable, and no relationship has been found between the severity of the hemorrhagic syndrome and the residual levels of FVII activity. The clinical picture can be very severe, with the early occurrence of intracerebral hemorrhages or hemarthroses, or, in contrast, moderate with cutaneous–mucosal hemorrhages (epistaxis, menorrhagia) or hemorrhages provoked by a surgical intervention. Finally, numerous subjects are completely asymptomatic despite a very low FVII level. Analysis of the gene coding for FVII led to the description of more than 130 different mutations, mainly punctual mutations, most of which are 'private' mutations, i.e., meaning each one has been identified in a single family. At present, concentrated FVII is given as replacement therapy but the indications remain difficult to discern prior to surgery for pauci- or asymptomatic patients.

Key words
coagulation factor VII, proconvertin, hemorrhagic syndrome

Name of the disease and it synonyms
Inherited coagulation factor VII (FVII) deficiency
Inherited proconvertin deficiency
Hypoproconvertinemia

Diagnostic criteria
An FVII activity level below that of pooled normal plasma (values usually between 70 and 140%) characterizes this deficit, which is usually symptomatic only for values below 30%.
The hereditary character of this deficiency can only be confirmed after two separate determinations of FVII activity and an in-depth familial inquiry.

Differential diagnosis
Positive diagnosis
A normal activated partial thromboplastin time associated with a prolonged Quick time is evocative of FVII deficiency, which is confirmed by dosage of the factor.

Differential diagnosis
These diseases include the acquired FVII deficiencies. The distinction is generally easy

when the FVII levels and/or the Quick time had previously been normal.
Acquired FVII deficits can be the consequence of several mechanisms:
-They are usually secondary to the excessive consumption and/or insufficient production of FVII, in which case they are associated with deficiencies of other factors. FVII, which is synthesized by the liver, is vitamin K-dependent and has a short half-life; the most common causes of an acquired FVII deficit are hepatocellular insufficiencies and hypo- or avitaminosis K. In addition, isolated and transitory diminution of FVII levels has been described during the course of severe infections.
- More rarely, the deficit observed can occur secondary to the presence of autoantibodies directed against FVII. Only several cases have been reported in the literature: one associated with bronchial carcinoma, another with medullary aplasia in a human immunodeficiency virus-infected individual positive for a lupus anticoagulant, and an apparently isolated case.

Prevalence
The prevalence has not been clearly established, but seems to be close to 1/1,000,000 in France.

Clinical description
The clinical signs are extremely variable and usually no relationship exists between the residual FVII activity level and the severity of the hemorrhagic syndrome. It is thus extremely difficult to define patients at risk of hemorrhaging.
Nevertheless, four clinical patterns can be distinguished.
The severe life-threatening form *is relatively rare, representing 10–17% of the cases, depending on the study, but it epitomizes all the severity of this deficiency. It is characterized by intracerebral hemorrhages, generally during the first week or months of life. Two cases arising spontaneously in adults have also been reported. The outcome is often fatal.*
The severe hemorrhagic form *accounts for 20% of the cases. It is characterized by hemarthroses, exhibiting the same manifestations as those seen in hemophiliacs with possible progression towards chronic arthropathy and severe joint degeneration. Unlike hemophilia, muscle hematomas are relatively rare.*
The late-onset, mild form *is the most common (50–60%). Its clinical manifestations include cutaneous–mucosal hemorrhages (epistaxis, menorrhagia, bleeding gums) and/or postsurgical hemorrhagic complications.*
The asymptomatic form is also detected in numerous patients who have less than 5% residual FVII activity, and even less than 1% for some patients.
Paradoxically, some patients with an FVII deficiency developed thromboses resembling myocardial infarction or pulmonary embolus.Management
The only available treatment is replacement of the missing factor with concentrated FVII from human plasma.
The following products can be used:
fresh frozen plasma,
PPSB or FVII concentrates;
activated recombinant FVII is currently being studied.
Theoretically, ***fresh frozen plasma*** can be used but, because of the short half-life of FVII, the repeated administrations would involve too large transfusion volumes.
PPSB is a fraction of plasma that contains in a concentrated form the four vitamin K-dependent factors at concentrations that can vary from one preparation to another. The recommended doses are empirical, ranging from 20 to 40 IU/kg every 6 hours. Its major inconvenience is the risk of disseminated intravascular coagulation (DIC) or thromboembolic complications.
FVII concentrates: The French Laboratory of Fractionation and Biotechnologies (LFB) distributes cryodessicated *FVII concentrates*, Factor VII LFB.
No consensus has been reached concerning the concentration of FVII to be maintained for hemostasis. Levels of 20–30% are sufficient to stop or prevent hemorrhage and a level of about 50% is recommended at the time of surgery. A single IU/kg of FVII can raise the plasma level by 2%. The plasma peak is obtained 30 min after the end of the injection. The half-life of FVII is around 4–6 h. This concentrate contains only very little or no activated FVII. No overdose has ever been reported. FVII inhibitors can appear (very rarely) in certain patients.
The recommended doses are the following: for a moderate hemorrhage: 15–20 IU/kg; for a severe hemorrhage: 30–40 IU/kg, repeated every 6–8 h; 1 h before surgery: 30–50 IU/kg. The FVII level should be measured immediately before the intervention. Subsequent doses of 20–30 IU/kg should be given every 6–8 hours so as to maintain a FVII level of 20–30% during the first few days following surgery and then controlled once a week.
Activated recombinant FVII (NovoSeven®) has recently been licensed in the treatment of bleeding episodes and in the prevention of bleeding during surgery or invasive procedures for patients with inherited FVII deficiency. The recommended dose is 15-30 µg/kg by bolus intra-venous injection every 4-6 hours until

haemostasis is achieved. Isolated cases of FVII deficient patients developing antibodies against FVII have been reported after treatment with NovoSeven®. These patients had previously been treated with human plasma and/or plasma-derived FVII. Therefore, patients with FVII deficiency should be monitored for FVII antibodies.

Etiology

Inherited FVII deficiency is an autosomal recessive trait. Only homozygotes and compound heterozygotes (that is, with two different mutations) develop hemorrhagic manifestations; heterozygotes are usually asymptomatic.

The gene coding for FVII is located on chromosome 13, a mere 2.8 kb upstream from the gene encoding factor X, and is 12,800 bases long. The DNA nucleotide sequence has been known since 1987. More than 130 different mutations in the gene coding for FVII have been identified to date; they are registered in the Europium database. The majority of these mutations are 'private' mutations, which means each one has been identified in a single family.

Two short deletions, of 15 and 17 bp, and a 15-bp insertion have been described; the other sequence modifications are punctual mutations. No large deletion has yet been reported. All types of punctual mutations are represented: non-sense mutations, false-sense mutations, splicing-site mutations and punctual insertions or deletions shifting the reading frame. The majority of these mutations are false-sense mutations distributed throughout all the exons, thereby emphasizing the importance of each of the FVII domains in the function and assembly of the molecule. The phenotypic consequences of each sequence change are highly variable, depending on the amino acid substituted. Unlike another vitamin K-dependent deficiency, hemophilia B, the non-sense mutations, introducing a premature stop codon, are relatively rare. Six mutations have been described in the promoter.

Exceptionally rarely, combined deficits can exist. The association of different inherited deficiencies can result from two mechanisms: the independent segregation of two types of deficits within a single family (the most frequent situation favored by consanguinity) or the dysfunction of a common gene or two genes topographically close (as seen in certain chromosomal anomalies). Thus, combined FVII and factor X deficiencies (either by deletion of q34 on chromosome 13 or by chance association within a family), or combined deficits of FVII and factor VIII, or factors II, IX, X and VII.

Biological methods of diagnosis

An FVII deficiency is suspected when a prolonged Quick time is associated with a normal activated partial thromboplastin time.

The chronometric dosage of FVII activity with known deficient FVII plasma identifies the isolated deficit. Normal values are comprised between 70 and 140%, defined in comparison to pooled normal plasma. For certain variants, the dosage may depend on the reagent (thromboplastin) used. The variant FVII Padua 1 is one of the most typical examples, yielding a level between 9 and 105%, depending of the reagent chosen. The use of recombinant human thromboplastin might provide a better standardization of the assay.

To characterize the deficiency, it is possible to conduct antigenic determinations by immunodiffusion, immunonephelometry and/or solid-phase immunoassays in order to differentiate qualitative deficits (immunological dosages higher that those of biological activity).

The differential diagnosis with the presence of anti-FVII antibodies can be made with a mixing test (addition of normal pooled plasma to the deficient one). The failure to correct the prolonged Quick time, after the addition of equal quantities of control plasma, should evoke the presence of a circulating anticoagulant.

Genetic counseling and prenatal diagnosis

Because of the marked heterogeneity of the phenotypes and genotypes seen in inherited FVII deficiency, genetic counseling will depend on the clinical repercussions of the disease in the family being considered. The existence of a first child with very severe manifestations, *e.g.*, intracerebral hemorrhages or repeated hemarthroses, can lead the medical team to propose prenatal diagnosis at the time of a subsequent pregnancy. On the other hand, the isolated discovery of a heterozygous FVII deficit in both partners of a childless couple raises numerous questions. At present, it is not possible to predict with certitude the phenotypic consequences of one or another mutation of the gene encoding FVII and even less the clinical repercussions of a genotypically compound heterozygote. Thus, in the absence of an affected first child, one must remain prudent not to propose systematic prenatal testing. It should be recalled that numerous carriers of a very severe FVII deficit are asymptomatic and lead a completely normal existence.

Unresolved questions and comments

The principal difficulty is the absence of a relationship between the severity of the hemorrhagic syndrome and biological findings. In addition, the genotype–phenotype interactions

have not yet been clearly defined. Indeed, it is difficult in the case of compound heterozygosity (the most frequent situation) to determine the contribution of each mutated allele to the phenotype. Numerous studies have enabled the characterization, in cellular expression systems, the *in vitro* properties of the different mutated proteins, but the transposition to the *in vivo* phenotype remains to be established. Thus, national and international registries of patients with FVII deficiencies are progressively being created with the aim of defining the clinical and biological subgroups, and better understanding the structure–function relationships of this protein.

Also unresolved is the therapeutic strategy to adopt for prophylactic substitution prior to surgery in patients with less than 5% FVII activity but hitherto asymptomatic. At present, no test to predict the hemorrhagic risk exists and the lack of consensus renders the therapeutic choices difficult.

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