PATHOGENESIS OF FACTOR VII DEFICIENCY

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Factor VII (FVII) deficiency is a bleeding disorder with an autosomal recessive inheritance pattern, in which reduced FVII activity in plasma is caused by quantitative or qualitative defects in the structure of the FVII protein. The global prevalence is approximately 1 patient per 500,000 population. About 99% of FVII circulates in plasma as an inactive zymogen, and only 1% is in the active form (FVIIa). The active form binds at the site of vascular injury with tissue factor (TF). The TF–FVIIa complex promotes further generation of FVIIa from the FVII zymogen and activates coagulation factors X (FX) and IX (FIX), which are involved in thrombin generation during the initiation phase of blood coagulation.

Keywords: *factor, blood coagulation, bleeding, hemorrhage, activity, laboratory diagnostics.*

Coagulopathies are a group of disorders that share a common underlying defect in blood clotting. They can affect patients of any age, sex, or ethnic background. Typically, these disorders occur in the context of other diseases and invariably worsen their course. Without timely medical intervention, hemostatic disturbances can lead to life-threatening complications.

Under normal conditions, blood coagulation is a protective mechanism activated only when blood vessels are damaged. When the vascular wall is disrupted or inflamed, coagulation factors are activated, leading to thrombus formation. Excessive thrombus formation can deplete clotting factors elsewhere in the vascular system, resulting in increased bleeding tendency [23,24].

Pathogenesis and Clinical Features of Factor VII (FVII) Deficiency

FVII deficiency is caused by rare defects in the F7 gene, which encodes FVII. The most frequently identified abnormalities occur in the F7 promoter. Inversions of intron 7 and exon 8 are found in approximately 30% of the general population and influence

baseline FVII activity. While these variations may contribute to the clinical and laboratory heterogeneity of FVII deficiency phenotypes, they are generally insufficient to reduce FVII activity to levels associated with bleeding.

The F7 gene is located on the long arm of chromosome 13 (locus 13q34) and consists of 9 exons. Its product, plasma factor VII (proconvertin), is a 406–amino-acid serine protease with a molecular weight of approximately 50 kDa. FVII is synthesized and secreted by hepatocytes into the plasma, and its normal production requires vitamin K. Plasma FVII concentration is approximately 0.5 μg/ml, with a half-life of 3–4 hours [20,21,22].

The primary function of FVII is to initiate blood coagulation. Upon vascular injury, tissue factor (TF) is exposed on the endothelial surface. The active form of FVII (FVIIa, ~1% of total circulating FVII) binds to TF, cleaving and activating factors IX and X, thereby initiating the extrinsic coagulation cascade. The resulting fibrin clot arrests bleeding [17,18,19].

Congenital FVII deficiency results from mutations in the F7 gene that either abolish protein production (type 1 deficiency) or produce a functionally defective protein (type 2 deficiency). To date, approximately 250 distinct mutations have been identified, affecting all exons but predominantly resulting in defects in the catalytic domain of the protein. Approximately 80% of these are missense mutations.

The main clinical manifestation of FVII deficiency is bleeding and hemorrhage, which can occur spontaneously or following trauma. The hemorrhagic syndrome most commonly presents with mucosal bleeding (including gastrointestinal mucosa), soft tissue hematomas, hemarthroses, and severe menorrhagia. Central nervous system (CNS) hemorrhages are reported in 3–10% of patients. Approximately 60% of cases are asymptomatic, with diagnosis often prompted by the incidental finding of prolonged prothrombin time (PT) [1,2,3,4,5,6].

Severe bleeding is typically observed when FVII activity is ≤1%. Patients with FVII activity >1% usually experience mild to moderate mucosal bleeding or remain asymptomatic. However, in some cases, severe hemorrhagic manifestations have been reported in individuals with FVII activity >20%, indicating a lack of direct correlation between laboratory values and clinical phenotype. Heterozygous carriers generally exhibit 40–60% FVII activity, with asymptomatic hypoproconvertinemia [7,8,9,10,11,12].

Stepwise Approach to Coagulological Examination in Suspected FVII Deficiency

Step 1: Initial Coagulological Screening Screening for suspected bleeding disorders includes:

- Activated partial thromboplastin time (aPTT)
- Prothrombin time (PT)
- Thrombin time (TT)

- Fibrinogen concentration (e.g., Clauss method)
- Bleeding time (standardized method, e.g., Ivy method)
- Instrumental assessment of platelet function

These tests allow determination of the type of coagulation disorder. In FVII deficiency, PT is prolonged, while aPTT, TT, fibrinogen concentration, bleeding time, and platelet function typically remain within normal limits.

Step 2: Verification of FVII Deficiency If PT is prolonged, FVII activity is assessed using a one-stage quantitative assay with FVII-deficient plasma included in specialized diagnostic kits [13,14,15,16].

Step 3: Differentiation of Qualitative vs Quantitative Defects To distinguish a qualitative (dysfunctional) FVII defect from a quantitative (deficient) defect, an enzyme-linked immunosorbent assay (ELISA) for FVII antigen may be performed.

Differential Diagnosis of Prolonged PT Any prolongation of PT warrants exclusion of acquired deficiencies of prothrombin complex factors, primarily caused by:

- Severe liver disease
- Obstructive jaundice
- Toxic effects of vitamin K antagonists
- Endogenous vitamin K deficiency

Isolated acquired FVII deficiency is rare and typically results from immune-mediated mechanisms, and can also be observed in systemic amyloidosis and nephrotic syndrome.

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