Factor VII deficiency

Factor VII deficiency (FVII deficiency) is a rare inherited bleeding disorder. It was first described in 1951 by Alexander et al and it has an incidence of approximately 1 in 500,000. Higher incidences have been found in certain populations where marriage between blood relatives is common.

Pathology
FVII is an important protein in the haemostasis process and plays a crucial role in initiating the coagulation process. It is synthesized by the liver and is present in the blood at very low concentrations (around 0.5 ug/ml). Individuals with FVII deficiency have defects of the FVII gene. The defects may result in a reduction of circulating levels of FVII, and/or a decrease in the ability of FVII to bind to TF. Complete absence of FVII activity in plasma is usually incompatible with life and individuals die shortly after birth due to severe bleeding.

Since binding of FVII to TF is necessary for initiation of coagulation and subsequent thrombin production. FVII deficiency leads to reduced thrombin formation, impaired thrombin-dependant platelet activation, insufficient fibrin formation and consequently clinical bleeding episodes.

Inheritance
FVII deficiency is an autosomal recessive inherited disease caused by a mutation of FVII gene, located on chromosome 13, one of the 22 pairs of autosomal chromosomes. It affects males and females in equal number. A FVII deficient person can be homozygous, double heterozygous or heterozygous for the mutations in the FVII gene.

Laboratory tests
FVII deficiency may be suspected on the basis of a prolonged prothrombin time. Confirmation of the diagnosis is generally based on repeated measurement of FVII activity showing levels below normal range, <50% of normal activity or <2% for the most severe defects. Activity of factors II, X and fibrinogen are normal in FVII deficient patients.

Unlike haemophilia, there is no correlation between the residual FVII activity in the blood and the severity of the bleeding. However, in general it can be observed that:
• Severe bleeding generally occurs when FVII activity levels are <2% of normal
• Bleeding episodes are less severe and less common in people with mild to moderate FVII deficiency (2-10% of normal).
• Normal haemostasis can be achieved with FVII activity as low as 10-15%

Bleeding episodes
The frequency and severity of bleeding episodes varies from person to person. Some people experience spontaneous, uncontrolled bleeding while in others the condition is less severe.

Spontaneous bleeding episodes include menorrhagia, epistaxis, easy bruising, gingival bleeding, muscle haematoma, haemarthrosis, gastrointestinal bleeding, haematuria and CNS bleeds (newborns particularly, due to birth-related trauma, often with tragic consequences)

Peri- and post-operative bleeding is also a major concern in patients with FVII deficiency.

The severity of bleeding is difficult to predict, but is most severe in people with the following characteristics

• FVII activity levels in the blood are either completely absent or present at a very low level (<2% of normal).
• Homozygousity or double heterozygousity for the FVII mutation
• Have certain mutations of the FVII gene (e.g. Cys135Arg substitutions or Ala294Val: 11125delC change)
• Have a personal or a family history of bleeding episodes.

Current treatment options
The goal of treatment for patients with FVII deficiency is to control bleeding episodes by substituting the missing clotting factor.

• Fresh Frozen Plasma (FFP): contains factor VII and may be used to treat FVII deficiency. However, plasma substitution can result in volume overload, transmission of blood-borne infections and transfusion reactions
• Intermediate Purity Factor IX Concentrates and PCCs: have been used for treating patients with FVII deficiency. In fact, these products are not calibrated for FVII concentrations. As the half-life of FVII is much shorter than that of other coagulation factors present, multiple doses of PCCs
may result in a build-up of other factors, increasing thrombotic risk. There have also been reports of thrombotic complications with intermediate purity FIX concentrates in people with FVII deficiency. Moreover, there are still some safety concerns about human viral transmission although these preparations are virally attenuated.

- **Plasma-derived Factor VII Concentrates**: FVII concentrates are prepared from pooled plasma. They are used for prophylactic treatment, as well as for controlling serious bleeding episodes, and bleeding during surgery. However, plasma-derived concentrates carry the risk of potential transmission of blood-borne pathogens.

- **NovoSeven®** is indicated for the treatment of bleeding episodes and for the prevention of bleeding in patients with congenital FVII deficiency undergoing surgery or invasive procedures. The recommended dosage is 15-30 ug/kg bw every 4-6 hours until haemostasis is achieved. Dose and frequency should be adapted to each individual. NovoSeven® has documented efficacy in patients with FVII deficiency for a wide range of bleeding episodes. NovoSeven® is free of human plasma and albumin, so there is no risk of human viral transmission.

- **Isolated cases of factor VII deficient patients developing antibodies against factor VII** have been reported after treatment with NovoSeven®. These patients have previously been treated with human plasma and/or plasma-derived factor VII. In two patients the antibodies showed inhibitory effect *in vitro*. Patients with factor VII deficiency should be monitored for factor VII antibodies.