

Factor VII deficiency

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BACKGROUND

Inherited Factor VII (FVII) deficiency is the most common of the rare autosomal recessive bleeding disorders, with an estimated prevalence of 1:500,000. It is more commonly seen in consanguineous marriages. More than 250 FVII gene mutations have been identified, the majority of which are missense mutations.

FVII is a vitamin K-dependent glycoprotein and initiates coagulation through binding to tissue factor at sites of vascular injury. Complete absence of FVII is believed to be incompatible with life. Knockout mice die perinatally from major abdominal and intracranial bleeding, after developing normally in utero. Mcvey et al (1998) described an infant that died 12 days after birth from massive intracerebral hemorrhage and was found to have a homozygous mutation resulting in complete absence of FVII. In comparison, a child with severe factor VII deficiency, who presented at age 3 years with recurrent bleeding (hematuria, hemarthroses, muscle hematomas, gastrointestinal bleeding) was treated with replacement therapy and did well.

DIAGNOSIS

In FVII deficiency, the prothrombin time (PT) is prolonged and corrects on mixing studies, with a normal activated partial thromboplastin time (aPTT). The diagnosis is confirmed with specific FVII assays. The source of the thromboplastin reagent used in the assay may produce varying results for certain FVII variants. Factor VII Padua variants have low FVII activity with rabbit tissue factor-based reagents but normal activity with human or ox tissue factor. Family studies may be useful in establishing the diagnosis.

Acquired causes of FVII deficiency should be excluded, including vitamin K deficiency, warfarin therapy, liver disease or long-term use of antibiotics. Other coagulation factors are usually decreased in such cases.

Acquired factor VII deficiency from inhibitors is very rare. Cases have been reported to occur spontaneously or with other conditions, such as myeloma, sepsis, aplastic anemia and as a paraneoplastic syndrome with atrial myxoma and Wilms tumor. To distinguish between

factor VII deficiency and the presence of an inhibitor to factor VII, mixing studies are useful.

CLINICAL FEATURES

Factor VII deficiency presents with a wide clinical spectrum, ranging from patients who are asymptomatic to life-threatening or fatal hemorrhage. Patients with severe deficiency less than 2% of normal, most often homozygous or compound heterozygous individuals, tend to have more severe bleeding, and may present similarly to severe hemophilia. Generally, patients with factor VII levels greater than 5%, tend to have milder bleeding patterns. Hemostasis is usually achieved by raising FVII activity above 10-15% of normal. However, factor VII coagulation activity does not always correlate with bleeding tendency for an individual patient; for example some patients with FVII levels greater than 20% report significant bleeding whereas few patients lacking factor VII function may not present with a history of bleeding.

The most frequent form of bleeding is mucocutaneous bleeding (bruising, epistaxis, gum bleeding). Menorrhagia is commonly reported in females. Some present with excessive bleeding after dental extraction and invasive procedures. Hemarthroses and muscle hematomas are less frequently seen. CNS bleeding is reported as well (4% to 17%). Postpartum bleeding is uncommon because FVII levels increase in late pregnancy.

FVII DEFICIENCY AND THROMBOSIS

Paradoxically, some patients with FVII deficiency develop thromboses, the mechanism of which is unknown. Venous thromboses are more commonly seen, usually deep vein thrombosis and pulmonary emboli. However, atypical sites such as portal vein or retinal vein thrombosis have been described. In most cases, an identifiable risk factor for thrombosis was found, including antiphospholipid antibodies, surgery and replacement therapy. FVII deficiency does not protect against thrombosis in high risk situations and so, antithrombotic prophylaxis should be used if the clinical scenario permits. If replacement therapy is considered,

then these patients should be carefully evaluated for their risk of thrombosis.

FACTOR VII DEFICIENCY AND SURGERY

Most studies have shown that the best predictor of bleeding is the clinical history. Patients who do not have a history of bleeding tolerate surgery well without replacement therapy. Barnett et al described two patients with baseline factor VII levels $\leq 1\%$ and no history of bleeding who without prophylactic replacement therapy did not bleed excessively with surgery.

Benlakhal et al reported perioperative bleeding in 15.3% of 83 patients with FVII deficiency (mean FVII level 5%; range 0.6 to 35%) who had undergone 157 surgical procedures without replacement therapy. FVII level $> 7\%$ had a negative predictive value of 94% for intra- or postoperative bleeding, while a level $< 7\%$ had a positive predictive value of 25% for such bleeding.

For patients undergoing surgery, important factors to consider in assessing the risk of perioperative bleeding include:

1. Surgical site (such as tonsillectomy, genitourinary, nose and oral surgery which are associated with an increased risk of bleeding),
2. History of severe bleeding symptoms (hemarthroses, severe hematomas, abundant epistaxis, CNS hemorrhage), and
3. Baseline FVII level.

Preoperative replacement therapy should be offered to patients undergoing major surgery with factor VII levels $< 10\%$ and those with levels of 10 to 30% with a positive clinical history. For most minor surgeries with FVII levels $< 10\%$ and mild to absent bleeding history, routine replacement therapy is not required but should be available in case of bleeding.

MANAGEMENT OF FVII DEFICIENCY

Replacement therapy can be achieved with several products. Recombinant factor VIIa is considered the optimal therapy and is used at a low dose 15 to 30 mcg/kg every 4 to 6 hours until hemostasis is achieved. If recombinant factor VIIa is not available, fresh frozen plasma (FFP) may be used, but is limited by its risk of volume overload due to large volumes required (15 ml/kg) which may also need to be administered every 4 to 6 hours due to short half-life of factor VII. Prothrombin complex concentrates (PCCs) may be used, but contains varying amounts of FVII and are associated with a risk of thrombosis.

Patients with minor bleeding usually do not require treatment. Local measures and use of antifibrinolytic agents may be adequate to stop bleeding in such cases. Patients with severe factor VII deficiency may benefit from secondary prophylaxis to prevent future severe or life-threatening bleeding; recombinant factor VIIa is the

preferred agent and is effective at doses of 20 to 30 mcg/kg given 2 to 3 times per week.

CONCLUSION

Factor VII deficiency is an autosomal recessive bleeding disorders with bleeding symptoms ranging from mild to severe. Although factor VII levels of 5% to 10% are usually sufficient to prevent spontaneous bleeding and levels of 10% to 25% are recommended for surgical hemostasis; plasma levels of factor VII do not always correlate with bleeding symptoms. Gathering a detailed patient's and family bleeding history is an important step when making decision about replacement therapy.

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