

Clinical picture and management of congenital factor VII deficiency

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Summary. In patients with congenital FVII deficiency, bleeding manifestations and clinical presentation vary widely, ranging from asymptomatic subjects to patients with haemorrhages that may cause important handicaps. Owing to menorrhagia, which occurs in about two-thirds of women of fertile age, bleeding is more frequent in women than in men. Gum bleeding and easy bruising are also more frequent in females. FVII:C levels are not a good predictor of bleeding tendency as there is a wide

overlap between bleeders and asymptomatic patients. We propose a three-grade system of classification based on clinical considerations. Therapy for congenital FVIII bleeding is discussed, with the advantages and disadvantages of each treatment, and the suggested single dose given.

Keywords: congenital FVII deficiency, haemostatic treatment

Although most cases display a mild clinical picture, bleeding manifestations and clinical presentation vary widely in congenital FVII deficiency, ranging from asymptomatic subjects to patients with haemorrhages that may cause important handicaps.

Bleeding manifestations recorded in the International Registry of Factor VII Deficiency (IRF7) are listed in Table 1. Nosebleed is by far the most frequent and is not gender-related. Other very common symptoms are postoperative, skin and gum bleeds. As for gender, women are more prevalent among bleeders: this is mainly attributable to menorrhagia, which occurs in about two-thirds of women of fertile age but gum bleeding and easy bruising are also more frequent in females. Severe and life-threatening haemorrhages are rare in general (about 5% of the bleeds) and occur most frequently during the first 6 months of life. In newborns (< 1 month) presenting bleeding manifestations were, as ranked for frequency, central nervous system (CNS), gastrointestinal (GI), cephalohaematoma and umbilical bleeding. Haemarthrosis and muscle haematoma in factor (F) VII-deficient patients

are not gender-related, clinically indistinguishable from those occurring in haemophilic patients, but not as frequent as in haemophilia.

Even when FVII:C levels are statistically lower in bleeders (Fig. 1), it is generally agreed that they do not predict the bleeding tendency in the individual patient. In fact, there is a wide overlap of levels between bleeders and asymptomatic subjects with FVII deficiency. Given the fact that FVII:C levels cannot distinguish between patients with different clinical severity, we have proposed a three-grade classification based on clinical elements: (i) the hallmark of the severe forms are CNS, GI bleeding and haemarthrosis, which are those with the earliest presentation; (ii) the intermediate forms are those characterized by a wide array of symptoms (three or more), with the exception of those defining the severe picture; and (iii) the mild forms are identified by a reduced number of symptoms (one or two), always with the exception of the severe ones. The prevalence is about of one-third for each of the classes of severity.

In general, FVII deficiency is associated, in the majority of patients, with a mild haemorrhagic disorder, characterized by haemorrhages of the mucous membranes and skin (e.g. epistaxis, menorrhagia, gum bleeding, easy bruising) (Table 1). Determinants of bleeding in the IRF7 database are: FVII mutation zygosity, FVII:C and age at first symptom.

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Table 1. Prevalence of bleeding related to gender in FVII congenital deficiency

Bleeding symptoms	Total (n = 228)		Males (n = 103)		Female (n = 125)	
	n	%	n	%	n	%
Epistaxis	85	37.3	43	41.7	42	33.6
Menorrhagia*	30	13.2	–	–	30	24.0
Post-operative bleeding	21	9.2	15	14.6	6	4.8
Easy bruising	18	7.9	7	6.8	11	8.8
Gum	17	7.5	6	5.8	11	8.8
Bleeding after dental extraction	11	4.8	4	3.9	7	5.6
Haemarthrosis	13	5.7	9	8.8	4	3.2
GI	10	4.4	5	4.9	5	4.0
CNS	8	3.5	6	5.8	2	1.6
Muscle haematomas	7	3.1	3	2.9	4	3.2
Haematomas	3	1.3	1	1.0	2	1.6
Haematuria	3	1.3	3	2.9	0	0.0
Rectal bleeding	3	1.3	3	2.9	0	0.0
Cephal haematoma	2	0.9	1	1.0	1	0.8
Postpartum bleeding	2	0.9	–	–	2	1.6
Retroperitoneal bleeding	2	0.9	0	0	2	1.6
Umbilical bleeding	2	0.9	1	1.0	1	0.8
Wound bleeding	2	0.9	1	1.0	1	0.8
Compartment syndrome	1	0.4	1	1.0	0	0.0
Haemoptysis	1	0.4	1	1.0	0	0.0

*Prevalence in the fertile age (10.5–50 years): 62%.

As stated above, postoperative bleeding is rather frequent in FVII deficiency, and the procedure most complicated by bleeding is dental extraction (Fig. 2). This is independent of the replacement therapy used, which means that for this disease, treatment materials and schedules for the prevention of bleeding are far from optimum.

Therapy

Unlike the other rare bleeding disorders, there are a number of treatment options for FVII deficiency: these are listed in Table 2, with the single recommended dosages.

Fresh-frozen plasma (FFP) can still be used for minor haemorrhages, if more potent treatment materials are not available, but, because of the risk

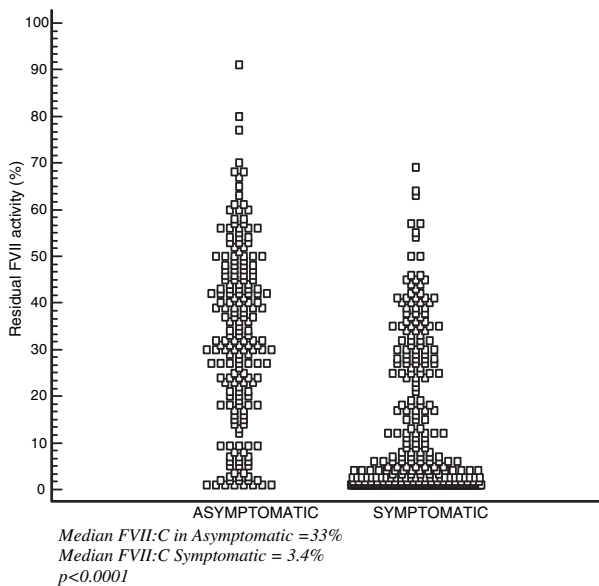


Fig. 1. Comparison of FVII:C levels between symptomatic and asymptomatic cases.

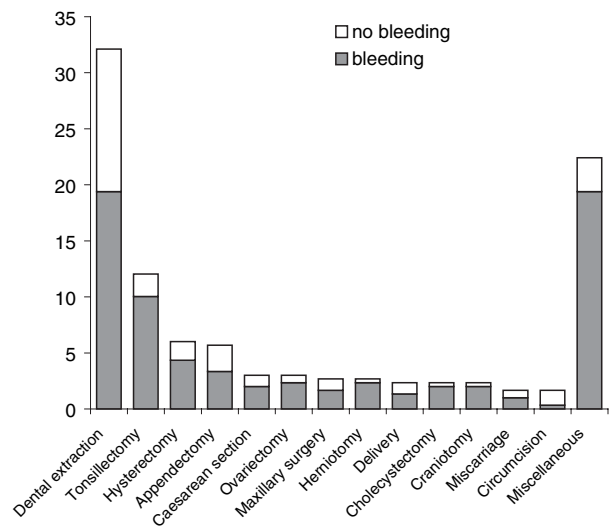


Fig. 2. Surgical procedures reported in the IRF7 (number) in relation to bleeding.

Table 2. Treatment options for inherited FVII deficiency

Material	Advantages	Disadvantages	Suggested single dose
FFP	Low cost and easily available; limited effectiveness	Circulatory overload; risk of viral transmission; unsuitable for surgery	8–10 mL kg ⁻¹
Virus-attenuated FFP*	Virally attenuated (reduced risk of viral transmission); limited effectiveness	Circulatory overload; unsuitable for surgery	8–10 mL kg ⁻¹
PCC (four factors)	Suitable for surgery; virally attenuated (reduced risk of viral transmission)	Other vitamin K-dependent factors (possibly activated) present in concentrations higher than FVII; high risk of thrombosis for repeated administrations	30–50 IU kg ⁻¹ †
pd-FVII§	Suitable for surgery; virally attenuated (reduced risk of viral transmission); effective.	Other vitamin K-dependent factors present in high concentrations; risk of thrombosis	20–40 IU kg ⁻¹ †
rFVIIa‡	Very effective for any indication (at very low doses); no risk of viral transmission.	Cost	15–30 mL µg ⁻¹

FFP, fresh-frozen plasma; PCC, prothrombin complex concentrates; pd-FVII, plasma-derived FVII concentrate; rFVIIa, recombinant activated FVII. *Two methods employed: solvent/detergents and methylene blue; †depending on the FVII concentration; ‡NovoSeven™, Novonordisk, Bagsværd, Denmark. §Three brands available: (i) Facteur VII, LFB, Lille, France; (ii) Factor VII concentrate, BLP, UK; (iii) Provertin™, Baxter Immuno.

of circulatory overload, it is not suitable for surgery. Plasma Complex Concentrates (PCCs) are effective in securing haemostasis without the risk of circulatory overload, but the risk of thrombosis becomes high, especially for repeated administrations and during surgery [1]. Plasma-derived preparations have been widely used in Europe for decades, [2] and are certainly effective for any indication; however, a few cases with thrombotic complications have been reported [1].

A recombinant-activated FVII preparation (rFVIIa; NovoSeven™) has recently been licensed in Europe for use in congenital FVII deficiency. In children and for prolonged administrations (e.g. prophylaxis or surgery) rFVIIa should be used as first-line treatment (single dose of 15–30 µg kg⁻¹ bw) [3,4]. For severe bleeds, multiple administration schedules (20–300 µg kg⁻¹) should be adopted, 4–6 h apart. For mild bleeds a single dose (15–200 µg kg⁻¹) should suffice. The average dose capable of normalizing the prothrombin time–international normalized ratio in severely affected patients was found to be 20 µg kg⁻¹ [3].

In treating a patient with FVII deficiency, the most important issue to be kept in mind is the very short half-life of the factor, between 1.5 and 3 h, with no apparent differences between the zymogen and the activated form [5]. This issue has two main practical implications: (i) it is difficult to prepare high-purity FVII concentrates because the relative concentrations of the vitamin K-dependent clotting factors are

higher than those of FVII and have similar physicochemical properties, and (ii) if the carer wants to use schedules based on less frequent administrations, then maintenance of the haemostatic levels of FVII requires higher dosages of FVII concentrates.

The latter issue confirms that the use of FFP is problematic, especially for surgical prophylaxis (low peaks of FVII and large volumes to maintain haemostatically effective trough levels); conversely, the use of PCCs or plasma-derived FVII concentrates makes it possible to attain haemostatically active levels of FVII but this may bring about an unnecessary rise of the other vitamin K-dependent proteins, which may cause a temporary thrombophilic state.

FVII deficiency in this regard should be considered similar to haemophilia B; in fact, thromboses have been reported, mostly in relation to surgery and the use of PCCs or plasma-derived FVII concentrates [1]. To reduce the risk of thrombosis in the surgical patient schedules based on the lowest haemostatically effective doses should be used (avoid very high FVII peaks!); a heparin prophylaxis is also advisable for patients at very high risk of thrombosis.

Among the potential side-effects, the occurrence of inhibitors should be considered. So far, only two cases of FVII-deficient patients with inhibitors have been observed and reported as severe side-effects, but not in formal medical publications. Another important side-effect to consider was the prevalence of viral infections due to the use of plasma and plasma derivatives, which was very high in this category of

patients until the introduction of viral-inactivation methods.

In conclusion, patients at high risk of bleeding (homozygotes or double heterozygotes) should be given replacement therapy for any haemorrhage or prophylaxis in the surgical setting. Dental extractions are also at high risk of bleeding, thus local or systemic haemostatic measures should be taken.

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