Hereditary factor VII deficiency in two siblings: two different clinical presentation

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ABSTRACT

Factor VII (FVII) deficiency is a rare bleeding disorder with a highly variable hemorrhagic predisposition. It is transmitted as an autosomal recessive and plays an important role in the initiation of blood coagulation forming a complex with tissue factor which activates FIX, FX and FVII zymogen. Prolonged prothrombin time with normal partial thromboplastin time indicates FVII deficiency. For the definitive diagnosis, the specific plasma FVII level should be investigated. FVII deficiency is expressed in different ways and leads to various clinical pictures. I reported two siblings with hereditary factor VII deficiency whose clinical presentations were different.

Key Words: Factor VII deficiency, Bleeding disorders, Hereditary, Childhood.

ÖZET

İki kardeşte herediter FVII eksikliği: İki farklı klinik tablo

Faktor VII (FVII) eksikliği, otozomal resesif geçiş gösteren nadir bir kanama hastalığıdır. FVII, doku faktörü ile kompleks teşkil ederek FIX, FX ve FVII zimogen aktivasyonunu sağlayarak eksternal koagülasyon çarkının bağlanmasında önemli rol oynar. Koagülasyon testlerinden protrombin zamanının (PT) uzun, parsiyel tromboplastin zamanının (PTT) normal olması FVII eksikliğini gösterir. Kesin tanı için plazma FVII seviyesinin ölçülmesi gereklidir. FVII eksikliği değişik şekillerde ortaya çıkar ve farklı klinik bulgulara sebep olur. Farklı klinik bulgularla seyreden FVII eksikliği olan iki kardeşi sunmak istedik.

Anahtar Kelimeler: Faktör VII eksikliği, Kanama bozukluğu, Kalıtsal, Çocukluk çağı.

INTRODUCTION

FVII (proconvertin, stable factor) deficiency is a rare autosomal recessive disorder of blood coagulation[1]. It's estimated prevalence is one per 300.000-500.000 in the general population[2,3]. Hereditary FVII deficiency was first reported by Alexander et al[4]. Since then, more than 200 cases have been described in the literature[5,6]. The factor VII gene is located on chromosome 13 (13q34)[7]. There is a rather poor correlation between clinical symptoms and FVII coagulant activity levels in plasma[3,8-10]. Clinically, cases range from asymptomatic to very severe hemorrhagic tendency[3].

Here, we are reporting a family whose first child suffered from serious bleeding diathesis whereas, second child and their parents were nearly asymptomatic related to a FVII deficiency.

CASE REPORT

Case 1

A 9-years-old boy was admitted to the our clinic with the complaints of soft tissue hematoma and recurrent hemarthrosis since early days of life. He was born following a full-term pregnancy. Her parents were first degree relatives. The mother has occasional mucosal bleeding, but the father has no bleeding problem. The physical examination of the child revealed a swollen and painful left ankle and a few ecchymoses on the anterior surface of the lower extremities.

Laboratory results were as follows: hemoglobin (Hb) 11.3 g/dL, hematocrit (Hct) 31.4%, white blood cells (WBC) 8600/mm^3 (58% neutrophils, 37% lymphocytes, 5% monocytes), normal erythrocyte morphology. Platelet count 357.000/mm^3, protrombin time (PT) 29.7 sec (control 11-15 sec), partial thromboplastin time (PTT) 38.4 sec (control 29-45 sec) and bleeding time 3.5 min, fibrinogen 515 mg/dL and FVII level was 9%. Based on these findings, a factor VII deficiency was considered and fresh frozen plasma (FFP) or FVII concentrate replacement was suggested in symptomatic periods. The parents were investigated regarding FVII levels, because of the mother's history of mucosal bleeding, consanguinity and autosomal recessive inheritance of FVII deficiency. FVII levels of father and mother were 48% and 37% respectively. According to these results the parents were considered to be carriers.

Case 2

A 6-years-old girl, the sister of case 1, was the product of the second pregnancy of the mother. Since, the etiology of the bleeding disorders had not been recognized in the first child, the mother was unaware of the FVII deficiency. Neither the patient nor his parents had any previous history of serious bleeding symptoms. On admission, her physical examination was unremarkable except from mild bleeding tendencies characterized by easy bruising on legs. Her laboratory examinations on admission revealed PT 36 sec (control 11-15 sec), PTT 39.2 sec (control 29-45 sec), Hb 10.4 g/dL, Hct 32.4%, MCV 72.5 fl, RDW 16%, Plt 329.000/mm^3, fibrinogen 228 mg/dL and plasma FVII activities 11% (control 50-150%).

We concluded that the patient had congenital factor VII deficiency.

DISCUSSION

In the present study, we reported a family whose first child with serious bleeding tendency had FVII level of 9% whereas, second child with mild bleeding tendency had FVII activity of 11% respectively and their parents were nearly asymptomatic related to a FVII deficiency.

Factor VII is a vitamin K-dependent glycoprotein which is essential for coagulation activation by the extrinsic pathway[11,12]. Upon vascular injury or following monocyte activation, tissue factor (TF) is exposed and forms a complex with FVII[13]. The TF-FVII complex initiates blood coagulation and is

capable of activating FIX and FX[13]. FVII deficiency is a rare, autosomal recessive, hereditary disorder and different genetic types have been described[3]. Both clinical expression and mutational spectrum are highly variable. Although we could not analyse our patients' molecular genetic defects, up to now more than 200 individuals with mutations in their FVII genes described in the world literature[14].

This illness is characterized by prolonged PT and normal PTT. The final diagnosis is established by quantitative factor VII assays. Patients have prolonged PT but normal aPTT and decreased plasma FVII activity.

In congenital FVII deficiency, bleeding can occur during any period of life and presents itself with quite variable clinical picture. Actually, there is a poor correlation between the FVII coagulant activity and the clinical bleeding tendency[10]. In general, a severe bleeding phenotype is only observed in individuals homozygous for a mutation in their FVII genes with FVII activities below 2% of normal[8,11]. Asymptomatic patients typically have FVII activity levels of > 20% and these patients may be heterozygotes, double heterozygotes or homozygotes for a mutation in their FVII genes[3]. On the other hand, mild FVII deficient patients, with FVII activity levels > 2%, may be double heterozygotes or homozygotes for FVII gene missense mutations[11]. Complete absence of FVII activity in plasma is usually incompatible with life and individuals die shortly after birth due to severe hemorrhage[11].

The patients with FVII deficiency usually have bleeding symptoms including extraction bleeding, menorrhagia, metrorrhagia, bruising and hemarthroses[3]. Central nervous system hemorrhages are not rare, and may develop during the newborn period or early childhood in about 15% of homozygous patients accounting for a high mortality rate[15]. Although, bleeding is frequently of mucocutaneous type, the whole array of haemophilic bleeding may also occur[15]. In the present study, first patient with severe bleeding tendencies had FVII activities 9% and second patient with mild bleeding tendencies had FVII activities 11%. Nonetheless, FVII activity level is a relatively poor guide to the severity of bleeding in the patients with congenital FVII deficiency[3,9,10].

My patient's mother occasionally experienced mucosal bleeding, but her father did not has a bleeding problem and both of them FVII levels were decreased. Bleeding problems are not often reported in patients having a factor VII activities level at 10-15% of normal or more[10].

We administered FFP in the symptomatic case (case 1). After FFP administration, the clinical status of the patient became stable. FFP, prothrombin complex concentrates or FVII concentrates can be employed in the management of these patients. Recombinant activated FVII (rFVIIa) is a very useful alternative and several patients have been treated successfully. From the available data it appears that rFVIIa is a safe and effective treatment modality for patients with congenital FVII deficiency[8]. Because of the short half-life of FVIIa, repeated doses have to be administered and continuous infusion may be even better[8].

Conclusively, these cases indicate that FVII deficient patients may admit with various symptoms. Some patients with FVII deficiency may be completely asymptomatic. In the case of prolonged PT but normal PTT, plasma FVII activity should be measured.

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