KAFKAS TIP BİLİMLERİ DERGİSİ
Kafkas Journal of Medical Sciences
Kafkas J Med Sci 2016; 6(1):64–68 • doi: 10.5505/kjms.2016.18894

OLGU SUNUMU / *CASE REPORT*

Inheritance of Factor VII and Protein S Deficiency Together with Factor V Leiden Mutation

Faktör VII ve Protein S Eksikliğinin Faktör V Leiden Mutasyonu ile Birlikte Kalıtımı

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ABSTRACT

Homozygous or heterozygous mutations of factor V Leiden (FV Leiden) and the thrombophilic factors like protein S deficiency are associated with venous or arterial thrombosis. In these patients, thrombosis may be seen even in the presence of coexistent congenital disorders of bleeding. Factor VII (FVII) deficiency is a rare autosomal recessive disorder of blood coagulation. When FVII deficiency occurs in combination with thrombophilic mutations, the symptoms of hemorrhagic diathesis are alleviated, like in other inherited hemorrhagic disorders. Herein, a 5-year-old and a 7-year-old, an asymptomatic sister and brother who respectively had 2 (FV Leiden mutation and protein S deficiency) and 1 (FV Leiden mutation) thrombophilic factors coexistent with FVII deficiency, are presented. The levels of FVII were 36% (N: 55%-116%) in the sister and 38% (N: 52%-120%) in the brother. FV Leiden mutation was homozygous and heterozygous in the sister and the brother, respectively. The protein S activity was 47% (N: 54%-118%) in the sister and normal in the brother. Familial work-up revealed FV Leiden mutation (heterozygous) in both parents and protein S deficiency in the mother [51% (N: 55%-160%)].

The paternal grandmother, who had died due to myocardial infarction, was learned to have had FVII deficiency. Neither of the siblings nor the grandmother had hemorrhagic diathesis. Even children with moderately decreased FVII levels may present with bleeding symptoms. Therefore, we think that the absence of hemorrhagic diathesis in our patients can be attributed to coinheritance of thrombophilic factors (protein S deficiency and/or FV Leiden mutation).

Key words: *factor V Leiden mutation; factor VII deficiency; protein S deficiency*

ÖZET

Faktör V Leiden (FV Leiden) mutasyonu ve protein S eksikliği gibi trombofilik faktörler, venöz ve arteriyel tromboz ile ilişkilidir. Bu hastalarda tromboz, eşlik eden bir kongenital kanama hastalığının varlığında bile görülebilir. Faktör VII (FVII) eksikliği, nadir rastlanan, otozomal resesif geçişli bir pıhtılaşma bozukluğudur. Faktör VII eksikliği trombofilik mutasyonlarla birlikte olduğunda, hemorajik diyatez belirtileri, diğer kalıtsal hemorajik hastalıklarda olduğu gibi hafifler. Burada, beş ve yedi yaşlarında olup, FVII eksikliği ile birlikte sırasıyla iki (FV Leiden mutasyonu ve protein S eksikliği) ve bir (FV Leiden mutasyonu) trombofilik faktör taşıyan semptomsuz bir kız ve erkek kardeş sunulmaktadır. Faktör VII düzeyleri kız kardeşte % 36 (N: 55–116) ve erkek kardeşte % 38 (N: 52–120) idi. FV Leiden mutasyonu sırasıyla kız ve erkek kardeşte homozigot ve heterozigottu. Protein S aktivitesi kız kardeşte % 47 (N: 54–118), erkek kardeşte normal idi. Aile çalışmasında, her iki ebeveynde FV Leiden mutasyonu (heterozigot) ve annede protein S eksikliği [% 51 (N: 55–160)] vardı.

Miyokard infarktüsünden ölen babaannede FVII eksikliği olduğu öğrenildi. Kardeşlerin hiçbirinde ve babaannede kanama diyatezi yoktu. FVII düzeyi orta derecede azalmış olan çocuklar bile kanama belirtileri gösterebilirler. Bu nedenle, hastalarımızda hemorajik diyatez olmamasının, bu hastalarda, trombofilik faktörlerin (FV Leiden mutasyonu ve protein S eksikliği) birlikte kalıtılmış olmasına bağlanabileceği düşüncesindeyiz.

Anahtar kelimeler: *Faktör V Leiden mutasyonu; Faktör VII eksikliği; Protein S eksikliği*

Introduction

Factor VII (FVII), a glycoprotein dependent on vitamin K, is an important factor in initiating the coagulation cascade. Following vascular injury, the tissue factor (TF) binds to the membrane and forms a calcium-dependent complex with either FVII (it is converted to FVIIa after a proteolytic degradation) or FVIIa (its serum level is extremely low) throughout the circulation. FVIIa, which binds to TF, activates factor X (FX) and accelerates the production of FXa. FXa and factor Va (FVa), its cofactor, convert prothrombin to thrombin. Additionally, the TF/FVIIa complex can also activate factor IX (FIX) to FIXa, which, after forming a complex with factor VIIIa (FVIIIa), contributes to FXa generation and thereby to thrombin formation via the intrinsic pathway. The activity of

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Geliş Tarihi: 13.02.2015 • Kabul Tarihi: 18.04.2016

the TF/FVIIa complex in the plasma is inhibited by tissue factor pathway inhibitors (TFPIs). TFPIs form complexes with FXa, FVIIa, and TF to express their activity. Finally, thrombin production is stopped by activated protein C (APC). APC, in turn, proteolytically inactivates FVa and FVIIIa, the basic cofactors of prothrombin-activating complexes[1].

FVII (a proconverting, stable factor) deficiency is a rare autosomal recessive disorder of blood coagulation. The FVII gene has been mapped on chromosome 13(13q34)[1].

The factor V Leiden (FV Leiden) mutation delays the inactivation of activated FV and thus leads to hypercoagulation[2]. Both heterozygous and homozygous forms of this disease are known to be associated with a high risk of recurrent thrombosis. Venous and arterial thrombosis may even be seen in the presence of coexistent congenital disorders of coagulation[2].

FVII deficiency in combination with thrombophilic mutations may lead to milder symptoms of bleeding diathesis, as in hemophilic disorders. Furthermore, mild to moderately low FVII levels do not always require bleeding symptoms to be absent or minor. Here, coinheritance of FV Leiden mutation and deficiencies of both FVII and protein S in a 5-year-old girl and coinheritance of FV Leiden mutation and deficiency of FVII in her 7-year-old brother are presented.

Case Report

A 5-year-old girl who presented for tonsillectomy was referred to our department since her *prothrombin time* was found to be prolonged in the preoperative evaluation and the prolongation persisted after intravenous vitamin K administration (3 mg). She had no history of prolonged bleeding from venipuncture sites and no history of easy bruising, spontaneous ecchymosis, pink-colored cutaneous eruption, gingival bleeding, epistaxis, hematuria, or hematochezia. She had no history of operative intervention. Her parents were second-degree relatives. Her mother (age: 35) had protein S deficiency [51% (N: 55%-160%)] and surprisingly had experienced prolonged bleeding only once, a few years ago after cardiac catheterization, while she had no history of menorrhagia or prolonged postpartum bleeding. She had not used oral contraceptives. The patient's brother, father, and other family members reported no history of prolonged bleeding. Her paternal grandmother had FVII deficiency without a history of prolonged bleeding and she had died of myocardial infarction at the age of 73. The lipid profile of the grandmother was not known.

The work-up of all family members revealed that the patient and her mother had protein S deficiency and her brother also had FVII deficiency (FVII level: 38%). The patient had homozygous FV Leiden mutation while her father, mother, and brother were heterozygous for the same mutation (Fig 1). Physical examination, complete blood count, blood smear, liver and renal function tests, and other laboratory results of both the patient and her brother were within normal limits. The laboratory results of hemostatic parameters of the patients and their parents, which were all tested at least twice, are presented in Table 1.

Discussion

It is well documented that FV Leiden or other thrombophilic factors like PT20210 G>A mutation or protein C deficiency coexisting with factor deficiencies like FVIII, FIX, or FVII may delay the onset of hemorrhagic symptoms and decrease the severity of clinical findings [2,3,4,5,6]. In vitro production of thrombin has been demonstrated to increase in these patients[2-7].

This report summarizes our evaluation of an asymptomatic girl with FVII deficiency and her family. That the family history displayed an FVII-deficient paternal grandmother who had no bleeding symptoms and developed myocardial infarction (arterial thrombosis) prompted us to evaluate the patient and her family for the main thrombophilic factors. Our work-up revealed that her brother was also FVII deficient and that the patient and her brother respectively had 2 (FV Leiden mutation and protein S deficiency) and 1 (FV Leiden mutation) thrombophilic factors coexistent with FVII deficiency; protein S deficiency with/without FV Leiden mutation prevailed in the family members. Although the literature contains no solid evidence to support a relationship between FV Leiden mutation and the risk of arterial thrombosis[8], there are a few exceptional cases with[9-12] or without[13,14] coexistent thrombophilic factors or disorders. However, we do not know if the paternal grandmother developed myocardial infarction as a rare manifestation of arterial thrombosis due to a possible FV Leiden mutation[13] or due to atherothrombosis, since she was learned not to have undergone replacement therapy or surgical operation before myocardial infarction.

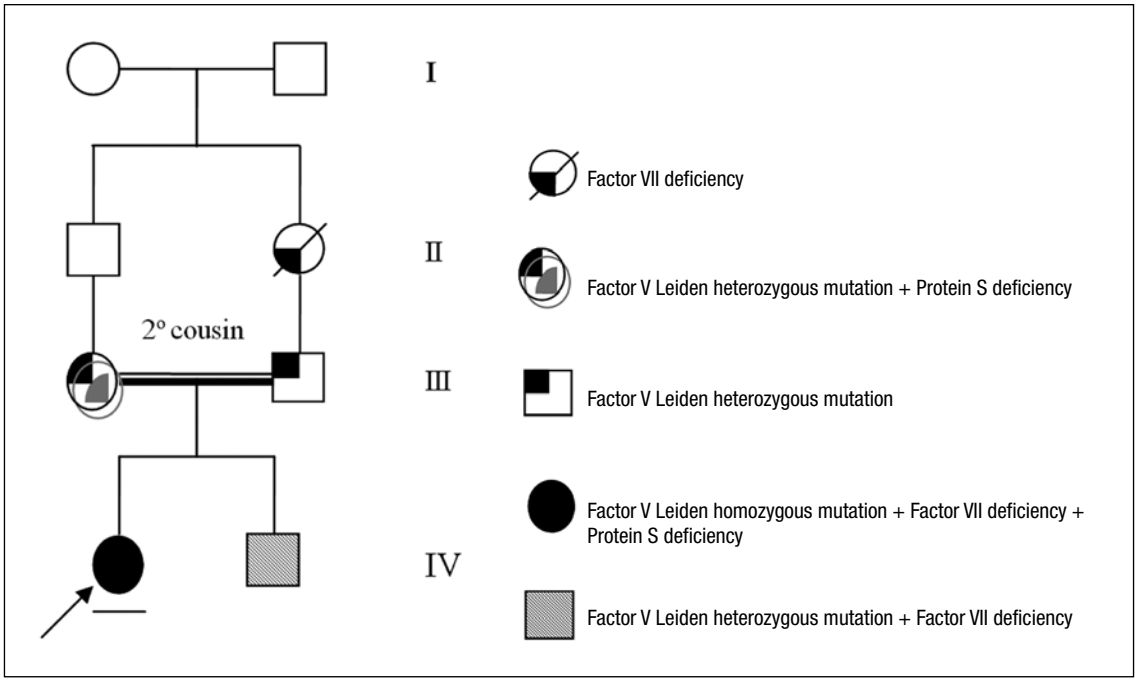

Figure 1. *The pedigree of the patient.*

Table 1. *Laboratory results of the patients and other family members*

	PT (11.1–13.2) sec	PTT (25–40) sec	INR (0.8–1.3)	Bleeding time (1–3')	ATIII (adult: 70–125%) (5 years: 82–139%)[24] (7 years: 90–131%)[24]	Protein C activity (adult:70–140%) (5 years: N 40–92%)[24] (7 years: N 45–93%)[24]	Protein S activity (adult:55–160%) (5 years: N 54–118%) (7 years: N:41–114 %)	FVII* (adults: 50–150%) (5 years: 55–116%) (7 years: 52–120%)	Factor V Leiden (1691 G>A)	Prothrombin gene mutation (20210G>A)
Father (age: 40 years)	12	28,3	1,179	147"	106,0	84,0	70,0	68,0	Heterozygous mutant	No mutation
Mother (age: 35 years)	11,7	27,9	1,145	150"	102,0	76,0	51,0	60,0	Heterozygous mutant	No mutation
Daughter (age: 5 years)	13.8	28.6	1.16	1'30"	120.0	70.0	47.0	36.0	Homozygous Mutant	No mutation
Son (age: 7 years)	14.8	25.6	1.25	1'45"	118.0	70.0	58.0	38.0	Heterozygous mutant	No mutation

As to the serum FVII level (10 to 50 IU/dL), both siblings were in the mild to moderate and heterozygous group, usually expected to be asymptomatic[15]. However, a characteristic of FVII deficiency is that a weak correlation exists between the degree of deficiency and the risk of bleeding[16,17]. Hence, FVII level did not differ between symptomatic and asymptomatic heterozygous FVII A294V subjects (FVII: 44+15%)[7]. Bhavnini et al.[18] reported 7 children with heterozygous FVII deficiency (FVII: 25%-56%), 6 of whom had spontaneous ecchymosis, 4 postoperative bleeding, and 1 epistaxis. FVII genotypes failed to explain the discrepancy between clinical severity groups[16]. In light of these findings, we can neither conclude that presence of FV Leiden mutation in both siblings and protein S deficiency in the sister alleviated the symptoms of bleeding nor that it affected the bleeding symptoms.

Eleven FVII-deficient patients out of 539 were reported to have developed thromboembolism [19,20]. All the tested patients with thromboembolism revealed normal

protein C, protein S, and ATIII levels and negative antiphospholipid antibodies and lupus anticoagulant[19,20]. Only one revealed an elevated homocysteine level[19]. On the other hand, a comparison of the prevalence of FV Leiden mutation, PT G20210A, FV HR2, and MTHFR C677T polymorphism and triggering risk factors for thrombosis (surgery and replacement therapy) between FVII-deficient cases with and without thrombotic events did not reveal any significant difference[19]. This shows that presence of FVII deficiency does not attenuate or change the effect of prothrombotic genes on the development of thromboembolism and does not offer protection when triggering factors for thrombosis like surgery and replacement therapy are present[18,21]. However, none of the 7 patients with FV Leiden mutation out of 25 FVII-deficient patients of Astermark et al.[20] experienced thrombosis. On the other hand, the overall protein C activity was found to be significantly lower in the FVII-deficient subjects than the normal controls[20]. In the literature, protein S deficiency in FVII deficiency is a new finding, showing that protein S may have a complementary role in the defect of the protein C pathway as a cofactor of protein C.

The protein C and S deficiencies may be compensatory hemostatic mechanisms alleviating the bleeding tendency. In the literature, we could not encounter any case with FVII deficiency carrying both thrombophilic factors of FV Leiden mutation and protein S deficiency together. In our patients, we could not evaluate antiphospholipid antibodies. Both siblings are being followed for possible bleeding diathesis and thromboembolism.

Coexistent FV Leiden mutation was found at frequencies ranging from normal (8.8%)[19,20] to elevated (14.2%) in patients with FVII deficiency (normal carriage incidence: 1%-8.5%; in Turkey: 7.9%)[2,22,23]. The frequency of the FV HR2 allele was very high in asymptomatic patients with FVII A294V mutation, unlike in the symptomatic ones (30% vs. 5.5%; normal population: 7.4%)[7]. PT G20210A mutation was reported at 4.4%, 0%, and 0% in FVII-deficient patients[19], in a subgroup of FVII-deficient patients with FVII Lazio mutation[2], and in a subgroup of FVII-deficient patients with FVII A294V mutation[7], respectively. Depending on the literature, we can state that the characteristic genotype/phenotype discrepancy in FVII deficiency may be due to compensatory hemostatic regulatory mechanisms such as increased frequency in FV Leiden mutation, although there are exceptions[20], FV HR2 allele[7], or decreased protein C level[20], which seem to differ as to the type of mutation.

The parents were accepted as heterozygous and the children as probably homozygous (less probably heterozygous) for FVII deficiency, and the daughter as protein S-deficient.

We think that protein S deficiency and other gene products or environmental factors to influence the activity or the turnover of the FVII molecule[7] should also be verified in greater numbers of FVII-deficient patients to establish the reasons for genotype/phenotype discrepancy.

Conflict of Interest Statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Acknowledgments

We thank Prof. Yahya Büyükaşık and Doç. Dr. Ercan Mıhçı for their kind comments and help.

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