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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Clinical Features, Laboratory Findings and Treatment of Patients with Rare Factor Deficiency: A Retrospective Single Center Experience

Nadir Faktör Eksikliği Olan Hastaların Klinik Özelliklerinin, Laboratuvar Bulgularının ve Uygulanan Tedavilerin Değerlendirilmesi: Retrospektif Tek Merkez Deneyimi

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ABSTRACT

Objective: Patients with a rare factor deficiency (RFD) may be asymptomatic or present with life-threatening bleeding. Studies have shown no direct relationship between factor activity level and bleeding severity, with difficulties being experienced in diagnosis and clinical follow-up. This study aims to contribute to Türkiye's data by evaluating the clinical and laboratory findings of the patients diagnosed with RFD and examined in this study.

Materials and Methods: The study involves 116 patients with an RFD diagnosis who were examined between 2005-2020. The study analyzes the patients' data retrospectively using patient files and the electronic registry system.

Results: The most common type of RFD is seen to be the factors VII (76%) and XI (8.6%) deficiencies. At the time of diagnosis, 50 (43.1%) patients were symptomatic, and 66 (56.9%) were asymptomatic. The most common complaints were epistaxis (n = 18 [15.5%]) and easy bruising (n = 8 [6.9%]). Five patients (three with factor VII and two with factor XIII deficiencies) were diagnosed with intracranial hemorrhaging (ICH). Of the patients, 12 (10.4%) had symptoms during the neonatal period. This study evaluated the coagulation systems of 97 patients suing thromboelastograms (TEGs), with 67 (69%) appearing normal and 30 (31%) showing symptoms compatible with RFD. When comparing the two groups, the TEGs were shown to be effective in determining bleeding tendencies, with Fisher's exact test showing a $p < 0.001$. Upon considering bleeding severity and factor level, prophylactic treatments were initiated in eight patients (7%), three of whom had a factor XIII deficiency, three with a factor X deficiency, one with a factor VII deficiency, and one with afibrinogenemia.

Conclusion: Patients with RFD should be noted to be able to be asymptomatic. TEG can be used effectively as a method for determining RFD patients' bleeding tendencies. Patients with signs of bleeding during the neonatal period can be monitored closely, and bleeding that may develop later can be prevented with early diagnosis.

Keywords: Rare Factor Deficiencies, Thromboelastogram, Epistaxis, Factor VII, Factor X, Factor XIII

ÖZ

Amaç: Nadir faktör eksikliği (NFE) olan hastalar asemptomatik olabildikleri gibi, hayatı tehdit eden kanama ile de başvurabilirler. Yapılan çalışmalarda faktör aktivite düzeyi ile kanama şiddeti arasında direkt bir ilişki gösterilememiştir. Tanı konulmasında ve klinik izlemlerinde zorluklar yaşanmaktadır. Bu çalışmamızda NFE tanısı ile takip ettiğimiz hastaların klinik ve laboratuvar bulgularını değerlendirerek Türkiye verilerine katkı sağlamak istedik.

Gereç ve Yöntem: 2005-2020 yılları arasında, NFE tanısı ile takip edilen 116 hasta çalışmaya alındı. Hastaların verileri hasta dosyaları ve elektronik kayıt sistemi kullanılarak retrospektif olarak incelendi.

Bulgular: En sık görülen FVII eksikliği (%76) ve FXI % (8,6) eksikliği idi. Tanı sırasında 50 (%43,1) hasta semptomatik, 66 (%56,9) hasta asemptomatik idi. En sık şikayet burun kanaması (n:18, % 15,5) ve kolay morarma (n:8, %6,9) idi. Beş hasta (FVII eksikliği (3), FXIII eksikliği (2)) intrakraniyal kanama (İKK) ile tanı almıştı. On iki (%10,4) hastanın yenidoğan (YD) döneminde semptomları vardı. Çalışmamızda 97 hastanın pıhtılaşma sistemi tromboelastogram (TEG) ile değerlendirildi ve 67'si (%69) normal, 30'u (%31) faktör eksikliği ile uyumluydu. İki grup karşılaştırıldığında kanama eğilimini belirlemede TEG'in etkin olduğu gösterildi (Fisher exact test: $p<0,001$). Kanama şiddeti ve faktör düzeyi dikkate alınarak 8 hastaya (%7) proflaktik tedavi başlanmıştı: FXIII eksikliği (3), FX eksikliği (3), FVII eksikliği (1) ve afibrinojenemi (1).

Sonuç: Nadir faktör eksikliği olan hastaların asemptomatik olabilecekleri unutulmamalıdır. Tromboelastogram hastaların kanama eğilimini belirlemede etkin biçimde kullanılabilen bir yöntemdir. Yenidoğan döneminde kanama bulgusu olan hastalar yakından izlenerek, erken tanı ile daha sonra gelişebilecek kanamaların önüne geçilebilir.

Anahtar Kelimeler: Nadir Faktör Eksikliği, Tromboelastogram, Burun Kanaması, Faktör VII, Faktör X, Faktör

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INTRODUCTION

Most inherited factor deficiencies comprise von Willebrand disease, hemophilia A, and B. Rare factor deficiencies (RFD) account for 3-5% of all inherited bleeding disorders. It is inherited in an autosomal recessive manner. It consists of fibrinogen, factor (F) II, FV, FVII, FX, FXI, FXIII, combined FV and FVIII (FV + VIII), and vitamin K-dependent factor deficiencies (1). The prevalence has been reported to be 1 in 2 million for FII and FXIII and 1 in 500.000 for FVII. Clinical findings vary in patients with RFD. Patients may be asymptomatic or present with life-threatening bleeding. They generally show a milder bleeding phenotype than patients with hemophilia. In addition, studies have not shown a direct relationship between factor activity level and bleeding severity (2). Because of these features, there are difficulties in their diagnosis and clinical follow-up.

While asymptomatic cases are diagnosed due to the length of coagulation tests performed before surgical procedures, patients with mild clinical findings present with complaints such as epistaxis and menorrhagia (1). Patients with severe bleeding phenotype present with intracranial hemorrhage, umbilical cord hemorrhage, and gastrointestinal (GI) bleeding in the neonatal period (1). Since prothrombin time (PT)/ activated partial thromboplastin time (aPTT) may be normal in mild factor deficiencies, it is recommended to order factor levels in case of clinical suspicion (1). Thromboelastogram (TEG) is an analysis that provides general information about the hemostatic system by evaluating the viscoelastic and mechanical properties of the clot. It is used to determine the severity of bleeding in patients (2).

Treatment varies depending on the clinical findings of the patient. Patients with severe bleeding phenotype receive prophylactic treatment after the treatment of acute bleeding. In patients with a mild bleeding phenotype, antifibrinolytic therapy in mucosal bleeding and replacement of the deficient factor in life-threatening bleeding are the main treatment modalities.

Because of its rarity, the clinical features of RFD are not clearly known. In this study, we aimed to contribute to the Turkish data by evaluating the clinical presentation findings, laboratory findings, factor activity levels, bleeding phenotype, and treatment modalities of patients with RFD in our hospital.

Table 1: Diagnoses of the patients

Type of deficient factor	n	(%)
Afibrinogenemia	2	(1.7)
Hypofibrinogenemia	6	(5.2)
FII	2	(1.7)
FVII	88	(75.9)
FX	4	(3.4)
FXI	10	(8.6)
FXIII	3	(2.6)
Combined (II, V, VII, X)	1	(0.9)

MATERIALS AND METHODS

A total of 116 patients diagnosed with RFD were included in the study, spanning from 2005 to 2020. The study used a retrospective patient file analysis and the electronic record system to gather relevant data. Recorded information encompassed family history, age of symptom onset, age at diagnosis, and bleeding episodes, as well as bleeding and prophylactic treatments. The bleeding phenotype of the patients was classified based on the recommendations of the European Network of Rare Bleeding Disorders (EN-RBD) group (3,4).

Patients were diagnosed based on clinical bleeding history, prolonged PT and aPTT, and low factor levels. Hemostasis screening tests, including PT, aPTT, fibrinogen, platelet count, and peripheral smear, were performed after detailed bleeding history and physical examination. In the presence of prolongation in PT and aPTT tests, factor levels that may be related were requested after excluding the presence of inhibitors by mixture test. Since PT and aPTT tests were not helpful in FXIII deficiency, factor levels were determined based on clinical findings. PT and aPTT levels were routinely checked before surgical procedures, and further investigations were performed in case of abnormality. The patients with factor activity <50% were included in the study. Depending on availability, factor levels were performed as one-step coagulation-based assays using commercial plasma devoid of the factor of interest on different coagulation analyzers (Beckman Coulter, Behring/Siemens, or Siemens Sysmex CA -1500 system). The modified Clauss method measured the fibrinogen level using a commercial reagent (Multifibren U of Behring/Siemens model). The cases in which the fibrinogen level could not be measured were considered afibrinogenemia, and those with a level below 100 mg/dl were considered hypofibrinogenemia. FXIII level was measured qualitatively by clot dissolution test method, and those with <5% were considered as deficiency (5). TEG was used to evaluate the

Table 2: Patients' complaints at the presentation

	n (%)
Asymptomatic	66 (57)
Epistaxis	18 (15.5)
Easy bruising	8 (7)
Intracranial hemorrhage	5 (4.3)
Prolonged bleeding after incision	5 (4.3)
Umbilical cord hemorrhage	4 (3.4)
Menorrhagia	4 (3.4)
Hematuria	3 (2.6)
GI bleeding	2 (1.7)
Intramuscular bleeding	1 (0.9)

ICH; intracranial hemorrhage; GI; gastrointestinal

Table 3: Characteristics of patients symptomatic in the newborn period and received prophylaxis

No	Diagnosis	Factor level (%)	Severity of bleeding	Complaint in diagnosis	Age at diagnosis (month)	Prophylaxis	Compatible with TEG Factor deficiency
1	Afibrinogenemia	1 mg/dl	Grade 3	Umbilical bleeding	1	No	Yes
2	FVII deficiency	2.3	Grade 3	Intracranial hemorrhage	1	Yes rfVIIa 30 mcg/kg 3 times a week	Yes
3	FVII deficiency	9.9	Grade 3	GI bleeding	1	No	Yes
4	FX deficiency	38	Grade 3	Umbilical bleeding	1	No	Yes
5	FXI deficiency	24	Grade 3	Umbilical bleeding	1	No	Yes
6	FX deficiency	1	Grade 3	GI bleeding	2	Yes Once a week 40 U/kg aPCC	Yes
7	FX deficiency	1	Grade 3	Umbilical bleeding	4	Yes Once a week 40 U/kg aPCC	Yes
8	Afibrinogenemia	1 mg/dl	Grade 3	Umbilical bleeding	5	Yes Twice a week 50 mg/kg fibrinogen concentrate	Yes
9	FXIII deficiency	< 5	Grade 3	Intracranial hemorrhage	8	Yes Once a month cryoprecipitate	Yes
10	FX deficiency	1	Grade 3	Umbilical bleeding	12	Yes Once a week 40 U/kg aPCC	Yes
11	FXIII deficiency	< 5	Grade 3	Umbilical bleeding	64	Yes Once a month cryoprecipitate	Yes
12	FXIII deficiency	< 5	Grade 3	Intramuscular	93	Yes Once a month cryoprecipitate	Yes

TEG; thromboelastogram, ICH; intracranial hemorrhage, GI; gastrointestinal, aPCC; activated prothrombin complex concentrate, rfVIIa; recombinant FVIIa

Table 4: Evaluation of bleeding severity

Clinical bleeding severity	n	(%)
Asymptomatic	56	48
Grade 1 (bleeding after trauma or medication)	7	6
Grade 2 (spontaneous minor bleeding; easy bruising, menorrhagia, epistaxis)	38	33
Grade 3 (spontaneous major bleeding; intramuscular, intra-articular, GI, umbilical bleeding)	15	13

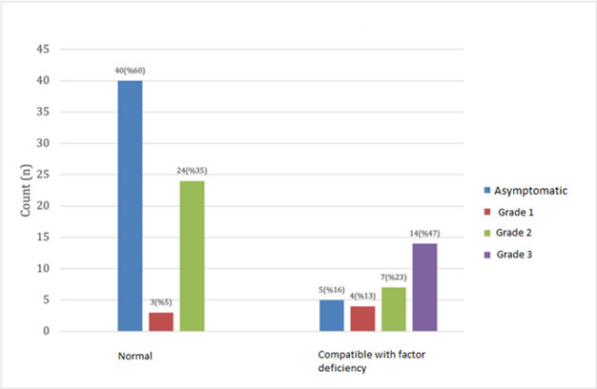
GI; gastrointestinal

bleeding status of the patients globally. The pathway from the onset of clot formation to fibrinolysis was evaluated with TEG. A haemoscope thromboelastography analyzer (Haemoscope, USA) was used for the TEG measurement.

Our study was approved by the Clinical Research Ethics Committee of S.B.Ü İzmir Dr. Behçet Uz Pediatrics and Surgery Training and Research Hospital (18.11.2021 / decision no: 351).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 22.0 (IBM Corp. Armonk, New York, USA) statistical package program. Descriptive statistics will be determined as a number of units (n), percentage (%), mean±standard deviation ($\bar{x}$±sd), median values, and minimum-maximum or 25th and 75th percentile values. The relationship between categorical variables was evaluated by chi-square, Yates correction (continuity correction), and Fisher exact test. A value of $P<0.05$ was considered statistically significant.



Graph 1:Distribution of clinical bleeding severity in patient groups with normal thromboelastogram results and results compatible with factor deficiency

Table 5: Characteristics of patients undergoing invasive procedures

Diagnosis	n	%
FVII deficiency	37	82.2
FX deficiency	3	6.7
FXI deficiency	3	6.7
FXIII deficiency	2	4.4
Invasive Procedure	30	66.7
Circumcision	3	6.7
Inguinal hernia op.		
Tooth extraction	2	4.4
Hypospadias op.	2	4.4
Tonsillectomy	2	4.4
Cystoscopy	1	2.2
Endoscopy	1	2.2
Operation of VUR	1	2.2
Excision of lung hydatid cyst	1	2.2
Pyloric stenosis		
Catheter angio	1	2.2
	1	2.2
Factor Application		
Yes	18	40
No	27	60
Bleeding		
Yes	0	0
No	45	100

VUR; vesicoureteral reflux

RESULTS

The median age at diagnosis was 74 months (min 1, max 197 months), and the median follow-up period was 24 months (min 1, max 183 months) in 116 patients (M/F:1.8). FVII deficiency (76%) and FXI deficiency (8.6%) were the most common (Table 1). Family history was positive in 27 patients. At the time of diagnosis, 50 (43.1%) patients were symptomatic, and 66 (56.9%) were asymptomatic. Factor levels were checked in 2 of the asymptomatic patients because of family history and in the remaining 64 patients because of prolonged PT/aPTT.

The most common complaints were epistaxis (n:18, 15.5%) and easy bruising (n:8, 6.9%) (Table 2). Five patients (FVII deficiency (3), FXIII deficiency (2)) were diagnosed with intracranial hemorrhage (ICH). Three of them had a spontaneous hemorrhage, and 2 had hemorrhage secondary to trauma. One patient (FXIII deficiency) developed ICH after diagnosis. All four patients with menorrhagia had FVII deficiency. Twelve (10.4%) patients had symptoms during the neonatal period (Table 3).

When the bleeding phenotype was analyzed, 38 patients (33%) had grade 2, 15 (13%) grade 3, and 7 (6%) grade 1 bleeding clinics (Table 4). Of the 15 patients with the grade 3 bleeding clinic, 6 had FVII deficiency, 3 had FX deficiency, 3 had FXIII deficiency, 1 had FXI deficiency, and 2 had afibrinogenemia. Eleven patients were symptomatic during the neonatal period. Fourteen patients had a TEG test at any time, all of which were compatible with factor deficiency.

Ninety-seven patients were evaluated by TEG, and 67 (69%) were found normal, and 30 (31%) were found compatible with factor deficiency. Of the 67 patients with normal TEG results, 40 (60%) were asymptomatic, and 27 (40%) had grade 1-2 bleeding (Graph 1). On the other hand, 25 (83.3%) of 30 patients with TEG results compatible with factor deficiency had a bleeding clinic, mostly grade 3 (Fisher exact test: $p<0.001$). The median PT value was 16.8 s (min-max: 10-120 s), and the median aPTT was 35 s (min-max: 25-144 s). The mean Hb level of the patients was 12.3 ± 1.07 g/dl (range: 9.8-15).

Cryoprecipitate was used in FXIII deficiency, activated prothrombin complex concentrate (aPCC) in FX deficiency, recombinant FVIIa in FVII deficiency, and ready fibrinogen concentrate in afibrinogenemia. Prophylactic treatment was started in 8 patients (7%) considering bleeding severity and factor level: FXIII deficiency (3), FX deficiency (3), FVII deficiency (1), and afibrinogenemia (1)) (Table 3). All of our patients who received prophylaxis received intravenous treatment in the hospital and did not have central venous catheters. Fifteen patients were using tranexamic acid for mucosal bleeding. Invasive surgical intervention was performed in 45 (39%) patients after diagnosis, and factor replacement was performed in 18 (40%) patients (Table 5). No perioperative bleeding was observed in any of the patients. None of the patients died due to bleeding during follow-up.

DISCUSSION

RFD is a disease group that currently lacks evidence-based guidelines for diagnosis, optimal treatment, prevention of bleeding episodes, and management of surgical procedures. Since it shows autosomal recessive inheritance, it is more common in countries where consanguineous marriages are common. Both genders are affected equally (2). In 116 patients in our study, males were affected 1.8 times more frequently than females. This was thought to be due to the high number of asymptomatic cases and coagulation screening tests routinely performed in boys before circumcision facilitated the diagnosis. Factor VII deficiency is the most common RFD, accounting for 38% of RFD. FII deficiency is the least common and constitutes

1.5% of all RFD (1). In our patient group, FVII and FXI deficiency were observed most frequently. In other studies conducted in Turkey, FVII deficiency was found most frequently, and FX and FXI deficiency were found in the second order (5,6). The frequency of RFD also varies according to geographical regions. A study conducted in Pakistan reported that FVII and fibrinogen deficiency were observed most frequently and secondly (7). In a study conducted in Iran, FVII, and FX, and in a study conducted in India, FX, FXIII, and FVII deficiencies were reported to be the most frequent (8,9).

Asymptomatic patients constituted a significant portion (56.9%) of our patient group, similar to other studies (5). In this asymptomatic group, the diagnosis was based on preoperative screening tests and family history (5). Clinical findings in patients with RFD vary regarding the bleeding site, bleeding severity, and onset age. In addition, the relationship between plasma factor level and bleeding clinic for each factor is variable (2). While there is a weak correlation between factor level and clinical phenotype in FVII and FV deficiencies, no correlation was found in FXI deficiency (4). In contrast, the relationship between fibrinogen, FX, combined FV and FVIII, and FXIII plasma levels and clinical bleeding severity is strong (4). The most common bleeding findings are epistaxis and menorrhagia (1). In our study, the most common complaints were epistaxis and skin and mucosa findings, including easy bruising. Menorrhagia is observed in 52% of girls with RFD (1). In our patient group, all girls with menorrhagia had FVII deficiency.

In RFD, there are two types of treatment modality: on demand and prophylactic. Generally, treatment is applied as bleeding occurs. In the treatment, pure factor concentrates are preferably used to replace the missing factor. However, specific factor replacement therapy is not possible for some factor deficiencies. Access to treatment options is limited, especially in developing countries. Fresh frozen plasma (FFP) and aPCC may have side effects. Although the risk of infectious viral infection in plasma-based therapies is currently low, other factor concentrates also have side effects, such as inhibitors, thrombosis, and hypersensitivity. FFP, cryoprecipitate, aPCC, recombinant FVIIa and plasma-derived factor concentrates are used in Turkey. Antifibrinolytic therapies can be used alone or in combination with factor replacement (3). Approximately 33% of mild mucosal bleeding can be controlled with tranexamic acid (10). The decision for prophylactic treatment is considered in cases where there is a risk of spontaneous bleeding, bleeding frequency is high, and bleeding continues to cause morbidity despite treatment (3). The dose and frequency of treatment vary depending on the desired minimal plasma factor level, the half-life of the factor, and the bleeding clinic (3). In our patient group, 8 (7%) received prophylactic treatment. All patients receiving prophylaxis were diagnosed with severe bleeding clinics in the newborn period.

Umbilical cord bleeding and epistaxis are frequently seen in afibrinogenemia. Primary prophylaxis is not routinely recommended (11). The desired plasma level for prophylaxis is 0.5-1 gr/l (3). Our patient who received prophylaxis presented with umbilical cord hemorrhage in the newborn period and was placed on prophylaxis.

The most common clinical findings in FVII deficiency are easy bruising and epistaxis (3). Based on the factor level, <10% is considered severe, 10-20% moderate, and >20% mild deficiency (1). Factor level alone is not decisive in the decision for prophylaxis. Prophylaxis is not routinely preferred because of the short FVII half-life. Secondary prophylaxis in severe cases is recommended as rfVIIa 20-40 mc/kg dose three days a week (11). The desired plasma FVII level with prophylaxis is 10-15% (3). In our study, one patient received secondary prophylaxis, which was initiated after ICH during the neonatal period.

FX deficiency is known to be associated with more severe bleeding phenotype compared to other patients with RFD. The most common symptoms have been reported as epistaxis, ICH, hematoma, and hemarthrosis (10). Plasma level <10% is considered severe, 10-40% moderate, and >40% mild deficiency (1). In our patient group, all four patients with FX deficiency presented findings in the newborn period and showed a grade 3 bleeding phenotype. Prophylaxis is administered once a week in severe cases. It may increase to 2 or 3 times a week depending on the bleeding clinic of the patient (12). In our study, three patients received plasma-derived concentrate containing FX prophylactically. All of them were diagnosed in the newborn period.

In FXIII deficiency, umbilical cord hemorrhage and intracranial hemorrhage are frequently observed (3). Plasma-derived and recombinant factor concentrate is available for the treatment. However, it is not accessible in Turkey. Primary prophylaxis is recommended in severe FXIII deficiency or the presence of family history. >80% of the patients have umbilical cord hemorrhage, and approximately 30% have ICH in the neonatal period (11). The patients with FXIII deficiency in our patient group received prophylaxis treatment with cryoprecipitate. One was diagnosed with ICH, one with umbilical cord hemorrhage, and one with intramuscular hematoma in the neonatal period.

Severe bleeding in RFD can be seen at an early age. Therefore, early diagnosis is of vital importance. In our study, ICH was seen in 6 patients. Of these, three were FXIII, and three were FVII deficiency. Twelve of our patients showed hemorrhage clinic in the newborn period. One study pointed out that patients with FX and FV deficiency were diagnosed at an earlier age (before three months) (5). In our study, 4 of 12 patients diagnosed in the neonatal period had FX deficiency. Umbilical cord bleeding was observed in 3 patients, and GI bleeding was observed in one patient.

TEG is a test that globally evaluates hemostatic activity and is very useful in determining in vivo hemostasis and clinical phenotype. It is also used in RFD (2,3). In our study, the coagulation system of 97 patients was evaluated by TEG, 67 (69%) were normal, and 30 (31%) were compatible with factor deficiency. When the two groups were compared, TEG was shown to be effective in determining bleeding tendency

(Fisher exact test: p<0.001). Since the relationship between factor activity level and bleeding severity is different for each factor, our study did not evaluate the relationship between factor levels and TEG results.

In conclusion, it should be kept in mind that patients with RFD may be asymptomatic. Therefore, patients with prolonged coagulation parameters should be investigated for RFD. TEG is a method that can be used effectively to determine the bleeding tendency of patients with RFD. Patients with bleeding findings during the neonatal period should be closely monitored, and early diagnosis may prevent bleeding that may develop later.

Ethics Committee Approval: This study was approved by the ethics committee of Clinical Research Ethics Committee of S.B.Ü İzmir Dr. Behçet Uz Pediatrics and Surgery Training and Research Hospital (18.11.2021 / decision no: 351).

Peer Review: Externally peer-reviewed.

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