ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of 36 Patients with Rare Factor Deficiency

Nadir Faktör Eksikliği Tanılı 36 Olgunun Değerlendirilmesi

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Abstract

Introduction: Rare factor deficiencies are predominantly autosomal recessively inherited disorders with a frequency of approximately 1: 500000 to 1: 2000000 in the general population. They account for 3-5% of all inherited coagulation disorders. In this study, we aimed to evaluate the demographic features and clinical findings of 36 patients who were followed up and treated with the diagnosis of rare factor deficiency.

Materials and Methods: A total of 36 patients aged between 0-16 years diagnosed with rare coagulation deficiencies were evaluated in terms of demographic, physical examination, clinical follow-up, and laboratory findings at the Dicle University Pediatric Hematology Unit. Ethics committee approval was obtained from Dicle University for the study on 16.03.2018 with decision no 115.

Results: Rare factor deficiencies were diagnosed in 36 (35 %) of 103 patients who were followed up with coagulation disorders. Hemophilia a, hemophilia b, and von Willebrand disease constituted 67 of our patients. Familial consanguinity was present in 75, 6 %, and positive family history was found at 16.6% of the patients. 11 (32.4%) of our patients were diagnosed under the age of one year. Most of our patients diagnosed with factor X deficiency (38.8%). The most common symptoms were mucocutaneous bleeding (50%). Intracranial hemorrhage was detected in 7 (%19,5) patients.

Conclusions: Early diagnosis and treatment are very important in the case of rare factor deficiency since severe bleeding complications such as intracranial hemorrhage may develop. Rare factor deficiencies are seen more frequently in places where consanguineous marriage is more common than the general population. Families should be informed about this issue, and family screening should be done early.

Keywords
Rare factor deficiency, bleeding, child

Anahtar kelimeler
Nadir faktör eksikliği, kanama, çocuk

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Öz

Giriş: Nadir faktör eksiklikleri; çoğunlukla otozomal resesif geçiş gösteren,prevalansı 1/ 500.000 -1/2.000.000 arasında değişen pıhtılaşma faktör eksiklikleridir. Kalıtsal pıhtılaşma faktör eksikliklerinin %3-5'ini oluşturmaktadır. Bu çalışmada, nadir faktör eksikliği tanısı ile takip ve tedavi ettiğimiz hastaların demografik özellikleri ve klinik bulguları değerlendirilmiştir.

Gereç ve Yöntem: Çalışmamızda, Dicle Üniversitesi Tıp Fakültesi Çocuk Hematolojisi ve Onkolojisi biriminde nadir faktör eksikliği tanısı ile takip ve tedavi edilen, yaşları 0-16 yıl arasında değişen toplam 36 hasta değerlendirilmiştir. Hastaların demografik özellikleri,klinik izlem sonuçları ve labaratuar verileri incelenmiştir.Çalışma için Dicle Üniversitesi'nden 16.03.2018 tarihinde 115 nolu karar ile etik kurul onayı alınmıştır.

Bulgular: Kalıtsal faktör eksikliği nedeniyle takip ve tedavi ettiğimiz 103 hastanın 36'sında (% 35) nadir faktör eksikliği tanısı mevcuttu. Hastalarımızın 67'sini

hemofili A, hemofili B ve von Willebrand hastalığı oluşturuyordu. Anne ve babaların akrabalık oranı % 75,6 olup,aile öyküsü %16.6 olarak bulunmuştur. Hastalarımızın 11'i (%32,4) bir yaşından önce tanı almıştır.Hasta grubumuzda %38,8 oranı (14 hasta) ile FX eksikliği en fazla görülmektedir.Tanı anında en sık başvuru semptomunu %50 ile cilt-mukoza kanamaları oluşturmaktaydı. Ciddi kanamalardan intrakranial kanama yedi (%19,5) hastada görülmüştür.

Sonuç: İntrakranial kanama gibi ciddi kanama komplikasyonlarıyla seyretmesinden dolayı nadir faktör eksikliğinde erken tanı ve tedavi çok önemlidir. Nadir faktör eksiklikleri, akraba evliliğinin fazla görüldüğü yerlerde genel popülasyona oranla sık görülmektedir. Ailelerin bu konuda bilgilendirilmesi,aile taramalarının erken dönemde yapılması gerekliliktir.

Introduction

Rare factor deficiency covers the deficiencies of F1 (fibrinogen), FII, FV, FV + FVIII, FVII, 4 FX, FXI, FXII, XIII, and combined deficiencies of vitamin K dependent factors (FII, FVII, 5 FIX, FX). It constitutes 3-5% of hereditary factor deficiencies (1). The prevalence is between 1: 500,000 and 1: 2,000,000. It is seen more often in countries where consanguineous marriage is common, such as Middle East countries like Turkey, Iran, and India (2,3). Clinical findings vary according to the deficient factor and factor level. In some cases, such as factor V, FVII, and FXI deficiency clinical manifestations and factor levels may not correlate (4,5). The patient with a rare factor deficiency apply to the clinic may present with early symptoms such as umbilical bleeding and intracranial hemorrhage that starts after birth, and may be asymptomatic and can be detected incidentally (2). Generally, rare factor deficiencies are characterized by milder signs symptoms than hemophilia (5,6). While joint bleeding is a major problem in hemophilia patients, mucosal bleeding is more common in rare factor deficiencies. However, FX deficiency may present with the clinic of severe intracranial bleeding (6,7). Rare factor deficiency is a special entity in terms of both diagnosis and treatment. The relationship between genotype and phenotype has not been determined yet. It is thought that the well-defined phenotype/genotype relationship will be guided in the treatment approaches by understanding the mutation types of rare factor deficiencies (8). In case of bleeding, factor concentrates, cryoprecipitate, or fresh frozen plasma(FFP)and prothrombin complex concentrate (PCC) are used. There are prophylaxis approaches for fibrinogen, FVII, FX, FXIII deficiencies. In addition to factor replacement therapy, antifibrinolytic agents can be given to prevent bleeding, especially in mucosal bleeding, or after dental treatments (7,8).

Materials and Methods

In this study, 36 patients with ages between 0-16 years who were followed up in Dicle University Faculty of Medicine Department of Pediatric Hematology and Oncology with the diagnose of factor FI (fibrinogen), II, V, VII, X, XI, XII, XIII, combined deficiency of vitamin K dependent factors (FII, FVII, FIX, FX), and combined deficiency of FV and FVIII were evaluated. The data were obtained by using patient follow-up files. Demographic features, age of presentation, and bleeding findings of the patients were recorded. The Complete blood count, coagulation, bleeding time, and factor level of our patients were analyzed in our hospital's laboratory. In rare factor deficiencies, the detection of plasma factor activities below the normal range (N: 50-150%) was considered diagnostic. Patients whose fibrinogen levels could not be measured were diagnosed with afibrinogenemia. Abnormal tests were repeated three different times to confirm the diagnosis. Mutation analysis of our cases could not be performed.

Ethics committee approval was obtained from Dicle University for the study on 16.03.2018 with decision no 115.

Results

Rare factor deficiency was diagnosed in 36 (35%) of 103 patients that followed up and treated due to hereditary factor deficiency. 67 of our patients were diagnosed with hemophilia 46 a, hemophilia b, and von Willebrand disease. Of those 36 patients, 14 were diagnosed with factor X deficiency(38.8%), eight with factor VII deficiency (22%), four with fibrinogen deficiency (11%), three with factor XI deficiency (8,3 %), two with factor V deficiency (5.5%), two with factor XIII deficiency (5.5 %), one with combined deficiency of factors associated with vitamin K (Factor II, FVII, FIX, FX deficiency) (2.7%), one with Factor XII deficiency (2.7%), and

one with combined deficiency of FV and FVIII (2.7%) (Table 1).

Of the 36 patients whose files were examined, 20 (55.5%) were female and 16 (44.5%) were male. The consanguineous marriage was determined in 27 (75.6%) families. Six of the patients had a history of bleeding diathesis (16.6%). Factor X deficiency in two siblings in two families, factor VII deficiency in two siblings in one family, factor XIII deficiency in two siblings in one family, FVII deficiency in two siblings in one family, and afibrinogenemia in two siblings in one family were detected (Table 2).

Mucodermal bleeding in 18 patients (50%), epistaxis in three patients (8.3%), gingival bleeding in five patients (13.8%), hematuria in one (2.7%), and gastrointestinal bleeding in four (11,1%) patients were detected. Five patients (13.8%) were diagnosed with examinations performed before planned surgery or after admission to the hospital for another reason. Factor activities (F: C) of 20 (55.6%) of our patients were below 5%. F: C levels of 10 (27.8%) patients were between 5-30%. F: C levels of six patients (16.6%) were> 30%. FX 65 level was below <5% in 13 patients (93%) with FX deficiency and intracranial bleeding was detected in these patients (Table 3).

Seven of the 36 patients had intracranial hemorrhage (19.4%). Five (35%) of 14 patients who were followed up with factor X deficiency had intracranial bleeding (Tables-4, 5). Two sisters also suffered intracranial hemorrhage during follow-up due to FXIII deficiency.

Five patients with FX deficiency who suffered from intracranial hemorrhage were treated with PCC / FFP without surgery. Patients with FXIII deficiency who suffered from intracranial hemorrhage were treated with the surgical operation + FFP. (Table 6).

Table 1. The distribution of patients according to factor deficiency

Factor deficiency	N (%)
FI (Fibrinogen deficiency)	4 (11,1%)
FII, FVII, FIX, FX deficiency	1 (2,8%)
FV deficiency	2 (5,5%)
FV and FVIII deficiency	1 (2,8%)
FVII deficiency	8 (22,2%)
FX deficiency	14 (38,8%)
FXI deficiency	3 (8,3%)
FXII deficiency	1 (2,8%)
FXIII deficiency	2 (5,5%)
Total	36 (100%)

N: total number of patients for each factor deficiency

Discussion

The prevalence of rare factor deficiency in the general population is quite low and constitutes approximately 3-5% of all hereditary factor deficiencies (1,5). In our study, 36 (35%) of 103 hereditary factor deficiency patients had rare factor deficiency. 67 of our patients were diagnosed with hemophilia a, hemophilia b, and von Willebrand disease. The 2014 report of WFH shows that there are 4860 hemophilia A, 1119 von Willebrand Disease, 878 hemophilia B patients, and 2290 patients with other bleeding diseases in our country (9). Genetic diseases with autosomal recessive transitions are more common in regions where consanguineous marriage is common. Therefore, we think that rare factor deficiencies are not rare diseases in our country with 36 patients who are followed up from a single center.

In our study, a consanguineous marriage rate of 75.6% was found in the parents of our patients. In our case series, the number of patients with rare factor deficiencies was higher than in other studies, we considered that this was due to the higher rate of

Table 2. Evaluation of patients factor activity according to factors deficiency

	Factors deficiency								
Factor activity	Fibrinogen N=4	FII, FVII, FIX, FX N=1	FV N=2	FV and FVIII N=1	FVII N=8	FX	FXI	FXII	FXIII
<%5	4	-	2	-	4	13	1	-	-
%5-30	-	-	-	1	4	1	2	-	2
>%30	-	1	-	-	-	-	-	1	1

N: total number of patients for each factor deficiency

consanguineous marriage and high birth rates in our region. In countries such as Iran, Egypt, and India, where consanguineous marriages are frequent, the prevalence of hereditary bleeding diseases is higher (2, 5). In our study, we found that the rate of consanguinity was 100% in patients with FX deficiency, 100% in patients with afibrinogenemia, and 50 % in patients with FVII deficiency. In the multicenter rare factor deficiency study conducted in our country in 2012, the rate of consanguinity was 25% in FVII deficiency, 26.1% in FV deficiency, and 27.3% in FX deficiency (10). In a single-center study, the rate of kinship was found to be 38.9% by Şalcıoğlu et al (11).

It was found that 89.1% of our patients were symptomatic, and five patients were diagnosed with examinations performed before planned surgery or after admission to the hospital for another reason.

Considering all of our cases, skin and soft tissue bleeding was 50%, intraoral bleeding was 13.8%, gastrointestinal system bleeding was 11.1%, epistaxis was 8.3%. The North American rare bleeding diseases study group shows that patients with rare factor deficiency have skin and mucous bleeding, unlike hemophilia patients (63%). The incidence of central nervous system (CNS) bleeding due to FX deficiency was 15%, and the rate was found to be 5-10% in fibrinogen, FII, FV, FVII, FXIII deficiencies. No symptoms were observed in 40% of homozygous FVII cases (6).

In 2004, Mannucci et al. conducted a study with 750 Iranian rare factor deficiency patients and found that the prevalence of symptoms was 66% for epistaxis,65% for menorrhagia, 38% for joint bleeding, 50 % for postpartum and surgical bleeding, 30% for intraoral bleeding, and 8% for CNS bleeding (2). In the study published by the North America Rare Coagulation Disorder Study Group in 2004, it has been reported that the most common diagnosis was factor VII deficiency in 294 patients with a diagnosis of rare factor deficiency, and the most common bleeding symptoms were skin and mucosal bleeding. It was reported that the most severe bleeding disorders were caused by factor X and XIII deficiencies (6).

In the multicentre study of Mariani et al. FVII deficiency study group published in 2005, it was reported that 24 volunteers with FVII: C values below 2% either did not show symptoms or showed a mild phenotype. Besides, it was seen that 16 volunteers with

Table 3. The demographic features of our patients

	N (%)
Gender	
Female	20 (55,5%)
Male	16 (44,5%)
Consanguinity	
Present	27 (75,6%)
Absent	9 (24,3%)
Age at diagnosis	
<1 years	311 (32,4%)
1-5 years	15 (40,5%)
<5 years	10 (27,1%)
Bleeding symptoms	
Symtomatic	32 (89,1%)
Asymtomatic	4 (10,9%)

Table 4. The distribution of bleeding symptoms according to factor deficiency at the time of diagnosis

	Fibrinogen deficiency (n=4)	FII, FVII, FIX, FX deficiency (n=1)	FV deficiency (n=2)	FV and FVIII deficiency (n=1)	FVII deficiency (n=8)	FX deficiency (n=14)	FXI deficiency (n=3)	FXII deficiency (n=1)	FXIII deficiency (n=2)
Skin, soft tissue (N)	4	1	-	-	2	9	-	-	2
Intraoral (N)	-	-	1	1	2	1	-	-	-
CNS (N)	-	-	-	-	-	-	-	-	-
Epistaxis (N)	-	-	1	-	1	1	-	-	-
GIS (N)	-	-	-	-	-	3	1	-	-
Hematuria (N)	-	-	-	-	1	-	-	-	-
Asymptomatic	-	-	-	-	2	-	2	1	-

GIS: gastrointestinal system, CNS: central nervous system, n: total number of patients for each factor deficiency, N: number of patients with the specific clinical presentation

Table 5. The distribution of patients with CNS according to factor deficiencies

Factor deficiency	CNS bleeding n (%)
Fibrinogen (N:4)	-
FII, FVII, FIX, FX (N:1)	-
FV (N:2)	-
FV and FVIII (N:1)	-
FVII (N:8)	-
FX (N:3)	5 (35,7%)
FXI (N:3)	-
FXII (N:1)	-
FXIII (N:2)	2 (100%)

N: total number of patients for each factor deficiency, n: number of patients with the CNS bleeding, CNS: central nervous system

Table 6. The distribution of patients according to factor deficiency

Factor deficiency	Bleeding	Prophylaxis
Fibrinogen deficiency	Fibrinogen concentrate	-
FII, FVII, FIX, FX deficiency	Vitamin K / Tranexamic acid	Vitamin K
FV deficiency	FF / Tranexamic acid	-
FV and FVIII deficiency	FVII/FFP / Tranexamic acid	-
FVII deficiency	rFVIIa / Tranexamic acid	-
FX deficiency	FFP / PCC/ Tranexamic acid	PCC
FXI deficiency	FFP / Tranexamic acid	-
FXII deficiency	-	-
FXIII deficiency	FFP / Tranexamic acid	FXIII concentrate

FFP: Fresh frozen plasma, rFVIIa: activated recombinant factor VII, PCC: Prothrombin complex concentrate

FVII: C values above 5% give serious symptoms (12). Factor level and severity of symptoms do not show any parallelism in factor VII deficiency. In our study, one of eight patients with Factor VII deficiency had a factor level below 2%. The patient was diagnosed after admission due to epistaxis. Mucosal bleeding was the main manifestation in the other seven patients and no serious bleeding was observed in any of our patients.

In our study, FX deficiency (38.8%) was the most common rare factor deficiency, and when all cases were examined, it was seen that the most common complaint was skin and soft tissue bleeding (50%). Generally, in the studies reported, factor VII cases had the biggest share among rare factor deficiencies (66.3%), while in our study, the frequency of factor VII deficiency was in the second place (22.2%).

In 2002-2008, Taskesen et al. conducted a study with 14 rare factor deficiency patients FX deficiency constituted 50% of the diagnose. The most common complaint was ecchymosis (13). In a multicenter study conducted in our country, the three most common deficiencies found among the rare factor deficiencies are FVII, FV, and FX deficiency, respectively (14). As can be seen, there are differences even in different regions of the same country.

Cases with deficiency of factor X may be asymptomatic or may be presented with skin and soft tissue bleeding, gastrointestinal bleeding, hemarthrosis, or hematoma. Intracranial hemorrhages and joint hemorrhages are seen less frequently. Cases of intracranial hemorrhage in factor X deficiency have been reported in different studies (15,16,17). In factor X deficiencies, CNS bleeding is reported at 9-26%, especially in the neonatal period (16,17). Karimi et al. (18) reported central nervous system bleeding as 10 (7.9%) in the rare factor deficiency group consisting of 126 patients. Of those patients five had the diagnosis of FVII, three had FXIII and 2 had FX deficiency. In our study, the Factor X level was found below 1% in 12 (85.7%) of 14 patients with Factor X deficiency. Intracranial bleeding was observed in five patients (35.7%). Skin and mucocutaneous bleeding was the most common symptom of admission. FX deficiency was present in two siblings of three families. In our region, both consanguineous marriage rates and birth rates are high.

FFP, PCC, and activated recombinant factor VII (rFVIIa) can be applied for the bleeding treatments of the patients. (19). In our opinion that prophylactic treatment should be applied in patients with severe bleeding such as intracranial bleeding. Our patients, five of whom had factor X deficiency, one had FV deficiency and two had FXIII deficiency, received prophylaxis and were followed up without any problems. Two sibling patients with FXIII deficiency received human coagulation factor XIII concentrate(Fibrogammin®) every four weeks, and five of our FX deficiency patients received PCC (Cofact®)prophylaxis once a week. An FV deficiency

patient with ovarian cyst rupture also received FFP prophylaxis once a week.

Rare factor deficiencies often show autosomal recessive inheritance and are important problems for societies like us since the rate of consanguineous marriage is high in our region. Early diagnosis and treatment prevent mortality and morbidity, and prophylactic procedures in required cases also increase the quality of life of patients significantly. In areas where hereditary blood disease carriers are frequent, measures such as raising awareness of the society, determining the carriers of the disease, and providing genetic counseling should be taken.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Dicle University for the study on 16.03.2018 with decision no 115.

Conflict of Interest: No conflict of interest was declared by the authors.

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