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Rare factor deficiencies in children: A review of 23 cases from a single center

Çocuklarda nadir faktör eksiklikleri: Tek merkezden 23 vakanın gözden geçirilmesi

[1]Özlem TERZİ

[1]Sanliurfa Training and Research Hospital, Pediatric Hematology and Oncology Clinic, Sanliurfa, Türkiye

Özlem Terzi: https://orcid.org/0000-0002-8449-4778

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ABSTRACT

Objective: The prevalence of rare factor deficiency (RFD) is one in 500.000-2.000.000 in the general population. Different symptoms may occur from mild or moderate bleeding to severe and life-threatening bleeding. This study aimed to evaluate children with RFD in a single Turkish center.

Materials and Methods: The records of children with RFD (Factor I, V, VII, X, XIII deficiency) were evaluated retrospectively.

Results: Twenty-three cases (70% female) were reviewed. The mean age of patients was 9.52 years at review, and mean follow-up was 66.3 months. The most common factor (F) deficiencies were FVII (35%) and FX (35%). Parental consanguinity was present in 65%. The most common symptoms were mucocutaneous bleeding and epistaxis. Regarding treatment, fresh frozen plasma (FFP) was given to two patients, FXIII concentrate was given to one patient, and prothrombin complex concentrate (PCC) was given to two patients. Prophylaxis was started in patients with recurrent bleeding. Of the 16 receiving prophylaxis, three received FFP, seven received recombinant coagulation factor VIIa, and six received PCC.

Conclusion: Treatment was given to a fifth of patients while nearly three-quarters received prophylaxis. As parental consanguinity was present in most of these patients, obtaining a detailed family history may aid in diagnosis.

Keywords: Child, factor, hemorrhage, rare factor deficiencies

ÖZ

Amaç: Nadir faktör eksikliğinin (NFE) prevalansı genel popülasyonda 500,000-2,000,000'de birdir. Hafif veya orta dereceli kanamalardan şiddetli ve hayatı tehdit eden kanamalara kadar farklı semptomlar ortaya çıkabilir. Bu çalışmanın amacı tek bir Türk merkezinde RFD'li çocukları değerlendirmektir.

Materyal ve Metot: Nadir faktör eksikliği (Faktör I, V, VII, X, XIII eksikliği) olan çocukların kayıtları retrospektif olarak değerlendirildi.

Bulgular: Yirmi üç olgu (%70 kadın) retrospektif olarak incelendi. İnceleme sırasında hastaların ortalama yaşı 9.52 idi ve ortalama takip süresi 66.3 aydı. En yaygın faktör (F) eksiklikleri FVII (%35) ve FX (%35) idi. Anne baba akrabalığı %65 oranında mevcuttu. En sık görülen semptomlar mukokutanöz kanama ve epistaksis idi. Tedavi açısından iki hastaya taze donmuş plazma (TDP), bir hastaya FXIII konsantresi, iki hastaya protrombin kompleks konsantresi (PCC) verildi. Tekrarlayan kanaması olan hastalara profilaksi başlandı. Profilaksi alan 16 kişiden üçü TDP, yedisi rekombinant pıhtılaşma faktörü VIIa ve altısı PCC aldı.

Sonuç: Hastaların beşte birine tedavi verilirken, yaklaşık dörtte üçüne profilaksi uygulandı. Bu hastaların büyük çoğunluğunda anne baba akrabalığı mevcut olduğundan ayrıntılı aile öyküsünün alınması tanıya yardımcı olabilir.

Anahtar Kelimeler: Çocuk, faktör, kanama, nadir faktör eksiklikleri

Sorumlu Yazar / Corresponding Author:
Özlem Terzi
Health Sciences University, Bakırkoy Training and Research Hospital, Pediatric Hematology and Oncology Clinic, Istanbul, Türkiye
Tel.: 00905305141545
E-mail: doktorozlem2020@hotmail.com

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INTRODUCTION

Rare factor deficiency (RFD) encompasses the deficiencies of clotting factors in the blood clotting cascade and includes factor I (FI; fibrinogen), FII, FV, FVII, FX, FXI, FXII, and FXIII. RFD constitutes only 3-5% of hereditary factor deficiencies,[1] and the prevalence is between 1:500,000 and 1:2,000,000.[2] The inheritance of RFD is usually autosomal recessive and thus affects both boys and girls.

RFD presents a heterogeneous clinical picture in affected patients, regardless of the degree of factor deficiency. Symptoms can range from mild or moderate bleeding to severe and life-threatening bleeding.[3] The most typical symptoms of RFDs involve the mucosal tissues or unexpected bleeding during invasive procedures. However, the most serious manifestations include intracranial hemorrhage. Prophylaxis may be considered in patients with recurrent severe bleeding.

Information about the epidemiology and clinical consequences of RFD in children is limited due to the condition's rarity.[4] In 2004 and 2007, data from the World Federation of Hemophilia and the European Rare Diseases Group were published and reported on RFD epidemiology, clinical and laboratory diagnosis, classification, and treatment options. It was reported that diagnosis of hereditary RFD can be made by prenatal amniocentesis and chorionic villus sampling. This early prenatal diagnosis will provide a decision about the continuation of the pregnancy and, if it is decided to continue, an opportunity for early intervention.[5]

Factor concentrates, fresh frozen plasma (FFP), and prothrombin complex concentrate (PCC) are used when bleeding occurs. Prophylaxis approaches for FI, FVII, FX, and FXIII deficiencies exist. In addition to factor replacement therapy, antifibrinolytic agents can be given to prevent bleeding, especially mucosal bleeding.[4]

The aim of this study was to evaluate the clinical and laboratory findings of children diagnosed with a rare coagulation defect in a single Turkish center.

MATERIALS AND METHODS

Ethics Committee Approval: This study was approved by the Saglik Bilimleri University, Bakirkoy Dr. Sadi Konuk, Training and Research Hospital Ethics Committee (Date: 03.05.2023, decision no: 2023-09-06). All procedures for studies involving human participants were carried out in accordance with the 1964 Declaration of Helsinki.

Patient Selection: All patients, aged between 0-18 years who were followed up because of a diagnosis of deficiency in any of the clotting factors (I, II, V, VII, X, XI, XII, XIII) in the Pediatric Hematology and Oncology Clinic of Sanliurfa Training and Research Hospital were identified. Of the total of 36 cases with a clotting factor deficiency, only those with an RFD, defined as a deficiency in any of FI, FII, FV, FVII, FX, FXI, FXII, and FXIII were included in the study. The data were extracted from patient follow-up files. Demographic features, age at presentation, family history, medical history of bleeding, laboratory assessments and prophylactic treatments of the patients were recorded. In RFDs detection of plasma factor activity below 50% was considered diagnostic. Patients whose fibrinogen levels could not be measured were diagnosed with afibrinogenemia. Abnormal tests were repeated on two occasions to confirm the diagnosis. Mutation analysis of the cases was not performed.

Statistical Analysis: Statistical Packages for Social Sciences, version 25, was used for data analysis (IBM Inc., Armonk, NY, USA). Descriptive statistical data are presented. As individual factor deficiency sub-group sizes were small, no comparative data analysis was attempted.

RESULTS

RFD was diagnosed in 23 patients and of these, 16 (70%) were female. At the time of data extraction, the mean age of the patients was 9.52 years the mean/median follow-up period was 66.3 months. Consanguineous marriage was present in 15 (65%) families. Twenty-two patients had a history of bleeding diathesis (95.6%). Factor deficiencies diagnosed were FVII (n=8, 35%), FX (n=8, 35%), FXIII (n=5, 22%) and one each with FI and FV deficiency (Table 1).

Table 1. The demographic features of our patients.

Variable	Result	n (%)
Age		9.52 years
Follow period		66.3 months
Gender	Female	16 (70)
	Male	7 (30)
Consanguinity	Present	15 (65)
	Absent	8 (35)
Bleeding symptoms	Symptomatic	22 (96)
	Asymptomatic	1 (4)
Factor (F) deficiency	FI (Fibrinogen deficiency)	1 (4)
	FV deficiency	1 (4)
	FVII deficiency	8 (35)
	FX deficiency	8 (35)
	FXIII deficiency	5 (22)

Abnormal bleeding had occurred in all but one of the patients, including mucodermal bleeding in eight patients (35%), epistaxis in seven patients (30%), hematoma in the knee in four patients (17%), gluteal bleeding in three patients (13%), umbilical cord bleeding in three patients (13%), hematuria in three (13%), anal bleeding in two patients (8.7%), hematoma in the elbow in two patients (8.7%), hematoma in the ankle in two patients (8.7%), abnormal menstrual bleeding in two (8.7%) and conjunctival bleeding in one patient (4.3%). The patient with FV deficiency

had no history of abnormal bleeding. Sites of bleeding by factor deficiency are shown in Table 2.
Factor activity was ≤5% in eight (35%) patients. Factor activity was 5-10% in 13 (56.5%), and activity in the remaining two patients was 10-20%. Factor activity (%) by factor deficiency is shown in Table 3.

Table 2. The distribution of sites of bleeding symptoms by factor deficiency.

Bleeding	**Factor Deficiency**				
	F I Deficiency n	F V Deficiency n	F VII Deficiency n	F X Deficiency n	F XIII Deficiency n
Mucodermal	-	-	4	3	1
Umbilical cord	-	-	2	-	1
Epistaxis	-	-	2	4	1
Anus	-	-	1	1	-
Hematuria	-	-	-	3	-
Hematoma/knee	1	-	1	1	1
Hematoma/elbow	-	-	-	2	-
Gluteal	-	-	1	-	2
Hematoma/ankle	-	-	2	-	-
Conjunctival	-	-	1	-	-
Menstrual	-	-	-	1	1
Asymptomatic	-	1	-	-	-

F: Factor; n: Number of patients.

Table 3. Factor activity (%) by factor deficiency in 23 patients with rare factor deficiency.

Factors	**Factor activity (%)**		
	≤5	5-10	10-20
FI (Fibrinogen) deficiency	-	1	-
FV deficiency	-	-	1
FVII deficiency	2	6	-
FX deficiency	3	5	-
FXIII deficiency	3	2	-

Regarding treatment, fresh frozen plasma (FFP) was given to three patients, factor XIII concentrate was given to one patient, and prothrombin complex concentrate (PCC) was given to two patients. Of the patients receiving prophylaxis, three received FFP, seven received recombinant coagulation factor VIIa, and six received PCC. In addition to factor replacement therapy, two patients were given antifibrinolytic drugs to prevent bleeding (Table 4).

Table 4. The distribution of patients according to factor deficiency.

Factor deficiency	**Treatment**	**Prophylaxis**
F I deficiency	FFP	-
F V deficiency	-	-
F VII deficiency	FFP, recombinant coagulation factor VIIa	FFP, recombinant coagulation factor VIIa
F X deficiency	PCC	PCC, antifibrinolytic drugs
F XIII deficiency	FFP, factor XIII concentrate	FFP

FFP: Fresh Frozen Plasma; PCC: Prothrombin Complex Concentrate.

Prophylaxis was started in patients with recurrent bleeding. Seven patients had not received prophylaxis. The distribution of factor activity and bleeding symptoms in patients receiving prophylaxis are shown in Table 5.

Table 5. Factor activity (%) and distribution of sites of bleeding symptoms in patients receiving prophylaxis.

Factor Deficiency	n	Factor activity (%)	Bleeding
F VII deficiency	7	7 (range 5-8)	Mucodermal, umbilical cord, epistaxis, anus, hematoma/ ankle, conjunctival
F X deficiency	6	7 (range 5-12)	Mucodermal, anus, hematuria, menstrual, hematoma/elbow
F XIII deficiency	3	5 (range 4-5)	Mucodermal, hematoma/knee, gluteal, menstrual

F: Factor; n: Number of patients.

DISCUSSION AND CONCLUSION

Due to the rarity, information on the epidemiology and clinical outcomes of RFD is limited. Hereditary bleeding diseases with autosomal recessive inheritance are more prevalent in regions with common consanguineous marriages.[6-8] The rate of consanguineous marriage in the parents of patients with RFD was reported to be 48.6% to 49.5% in Turkey.[9,10] In the present study, a consanguineous marriage rate of 65% was found in the parents of our patients. In our case series, consanguineous marriage rate was higher than in other studies. This may be because there is a high proportion of consanguineous marriage in the catchment population of the study center. The rate of consanguineous marriage in Sanliurfa is 18.4%.[11] However, Elhadi et al. reported a consanguineous marriage rate of 93.6% in their study of 43 RFDs in Sudan.[12] Consanguinity marriage is common in Africa, and the estimates range from 29 to 49% of all marriages in Africa.[13]

Hemarthrosis and intramuscular bleeding are the most common symptoms in patients with hemophilia, while mucocutaneous bleeding is more common in RFDs. It has been reported that the most common type of bleeding in RFD patients was mucosal bleeding, affecting 40% to 67.7%.[14-16] In the study of Akdeniz et al., most bleeds were of mucosal origin (67.7%).[14] Park et al. reported that the most frequent symptoms were mucosal tract bleeding (40%) similarly.[15] In the study of Gelen et al., this rate is 53%.[16] In keeping with these reports, the most common site of bleeding in the present study was the mucosa (35%), followed by epistaxis (30%), although seven (30%) had also had hemarthrosis.

The two most reported deficiencies among the RFDs are FVII and/or FXI deficiency.[3,17-19] In the present study, FX and FVII deficiency (35% and 35%) were the most common RFD. In the past, prediction of the severity of bleeding was based on factor activity levels in RFD.[3] However, studies have shown that factor activity levels and clinical manifestation of bleeding are not always compatible. In FI, FII, FX, and FXIII deficiency, the correlation between factor activity level and the severity of bleeding was strong, but this does not hold for FV, FVII, and FXI deficiency.[3] Khudhair et al. reported that clinical manifestations of FVII deficiency are variable and not necessarily correlated to the FVII level.[18] In the study, five out of 10 patients with FVII level < 1% have either mild to moderate disease without complications, while six out of 14 patients with FVII > 1% had at least one episode of severe bleeding.[18] Of note, no serious bleeding was observed in any of the patients in the present study, despite 3/8 of the patients with FX deficiency having activity <5% and 3/5 with FXIII deficiency also having <5% activity. In addition, the factor activity of patients with recurrent bleeding was found in the 4-12% range.

There is no accepted therapeutic strategy for RFDs. Management of RFDs is mainly based on expert consensus rather than evidence-based guidelines. Patients with RFD may have a broad spectrum of clinical symptoms, ranging from mucocutaneous bleeding to life-threatening hemorrhages, such as those occurring in the central nervous system. Early diagnosis and treatment prevent mortality and morbidity, and prophylactic procedures in required cases significantly increase patients' quality of life. FFP, PCC, and activated recombinant factor VII (rFVIIa) can be given to treat/prophylaxis bleeding in affected patients.[4,20,21] In our study, prophylaxis with FFP, PCC, or rFVIIa was applied to sixteen patients with FVII, FX, and FXIII deficiency because of recurrent bleeding. No complications or bleeding were observed in our patients, and they were followed up without any problems at the time of writing; due to this, we think that prophylaxis is appropriate after recurrent bleeding.

In conclusion, RFDs are rare autosomal recessive conditions. However, in regions with a high degree of consanguineous marriage, the prevalence of RFD may be higher, and it becomes a significant clinical problem. There must be awareness of bleeding diathesis in the general population, especially in re-

gions with an increased incidence of consanguineous marriage. It should also be remembered that there may not be a direct relationship between the factor activity level and the severity of bleeding experienced by affected patients. This study had some limitations. These include the study's retrospective nature, the small size of the longitudinal cohort, and the fact that genetic mutation analysis was not performed in any patient.

Ethics Committee Approval: Our study was approved by the Saglık Bilimleri University Bakirkoy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (Date:03.05.2023, decision no: 2023-09-06)

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

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