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Rare Factor Deficiencies: A Retrospective, Single-center Cohort Study

Nadir Faktör Eksiklikleri: Retrospektif, Tek Merkezli Kohort Çalışma

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ABSTRACT

Objective: Rare factor deficiencies (RFD) include fibrinogen and factor (F) II, FV, combined FV and FVIII, FVII, FX, FXI, and FXIII deficiencies. Although patients with RFD may present with severe hemorrhage, little is still known about this patient group. Additionally, mortality and morbidity also increase due to the limited available knowledge concerning diagnostic and therapeutic methods and surgical approaches. Herein, we report the demographic features, clinical follow-up, surgical approaches, and treatment of patients with RFD.

Methods: We retrospectively evaluated 37 patients with RFD. Patients' demographic characteristics, age at presentation, type of bleeding at diagnosis, clinical findings, surgeries performed, and surgical approaches were recorded.

Results: In this study, 64.8% of the patients were males and 35.2% were females. The most common factor deficiency was FVII deficiency (29.7%). Parental consanguinity was detected in 48.6% of cases. Adenoidectomy was performed on 27% of patients with FVII deficiency. Circumcision was performed on 67% of patients with FXI deficiency, 27% of patients with FVII deficiency, and 20% of patients with FV deficiency. Fresh frozen plasma, fibrinogen concentrate, or rFVIIa combined with tranexamic acid were administered before surgery. No post-operative complications were observed.

Conclusion: RFDs are prevalent due to the increased frequency of consanguineous marriages, and the diagnosis of coagulation disorders is substantially delayed in Turkish children. Since the clinical findings of RFDs are not obvious, patients in the preoperative period must be assessed with RFD in mine. We think that this paper will contribute to the diagnosis and treatment of RFD and to the surgical approaches.

Keywords: Rare factor deficiencies, surgery, factor

ÖZ

Amaç: Nadir faktör eksiklikleri (NFE) fibrinojen ve faktör (F) II, FV, kombine FV ve FVIII, FVII, FX, FXI ve FXIII eksikliklerini içerir. Şiddetli kanama bulguları ile ortaya çıkabilecek bu hasta grubu hakkında yeterli bilgi mevcut değildir. Tanısal ve terapötik yöntemler ve cerrahi yaklaşımlar hakkındaki mevcut sınırlı bilgi nedeniyle mortalite ve morbidite de artmaktadır. Burada demografik özellikler, klinik takip, cerrahi yaklaşımlar ve NFE'li olguların tedavisi sunulmaktadır.

Yöntemler: Otuz yedi NFE hastası retrospektif olarak değerlendirildi. Hastaların demografik özellikleri, başvuru yaşı, tanıdaki kanama tipi, klinik bulgular, yapılan operasyonlar ve cerrahi yaklaşımlar kaydedildi.

Bulgular: Hastaların %64'ü erkek, %35,2'si kadındı. En sık görülen faktör eksikliği FVII eksikliği (%29,7) idi. Olguların %48,6'sında ebeveyn akraba evliliği saptandı. FVII eksikliği olan hastaların %27'sine adenoidektomi uygulandı. Sünnet, FXI eksikliği olan hastaların %67'sine, FVII eksikliği olanların %27'sine, FV eksikliği olanların %20'sine uygulandı. Taze donmuş plazma, fibrinojen konsantresi veya rFVIIa, ameliyattan önce traneksamik asit ile birlikte uygulandı. Ameliyat sonrası komplikasyon gözlenmedi.

Sonuç: NFE'ler, sık akraba evliliği nedeniyle yaygındır ve koagulasyon bozukluğunun teşhisi büyük ölçüde gecikmektedir. NFE'lerinin klinik bulguları açık olmadığından, preoperatif dönemde hastaların NFE açısından değerlendirilmesi gerekir. Bu yazının NFE tanı ve tedavisinin yönetimine ve cerrahi yaklaşımlara katkıda bulunacağını düşünüyoruz.

Anahtar kelimeler: Nadir faktör eksiklikleri, cerrahi, faktör

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INTRODUCTION

Rare factor deficiencies (RFDs) include congenital fibrinogen and factor (F) II, FV, combined FV and FVIII, FVII, FX, FXI and FXIII deficiencies other than hemophilia A, hemophilia B, and von Willebrand's disease. A deficiency in any of the above-mentioned coagulation factors may result in a coagulopathy, leading to either spontaneous or post-traumatic and post-operative hemorrhages. Deficiencies of FVIII and FIX, also known as hemophilia A and B, are the most common, with a prevalence of 1:5,000 and 1:30,000 males, respectively; together with von Willebrand's disease, they account for 95%-97% of all coagulopathies (1). On the other hand, the remaining deficiencies, known as rare coagulation disorders (RCDs), are much less prevalent, with rates ranging from 1:2 million for FII and FXIII deficiencies to 1:500,000 for FVII deficiency, in the general population (2). However, all these RCDs represent an important challenge for clinicians, especially in countries where consanguineous marriages are frequent. RCDs are characterized by a wide variety of symptoms ranging from mild to severe, which can vary significantly from one disorder to another and from one patient to another. Generally, the most typical symptoms of all RCDs include mucosal tract bleedings and excessive bleeding during invasive procedures, delivery in women, and circumcision in boys. In addtion, other life- and limb-endangering symptoms such as central nervous system (CNS) bleeding and hemarthroses are mostly present only in afibrinogenemia and FX and FXIII deficiencies (3). This clinical heterogeneity, combined with the smaller number of patients affected with RCDs compared with hemophilias, led to a lack of studies that aim to understand how to recognize and diagnose a RCD. As a result, this lack of knowledge led to a delay in the design and production of adequate therapeutic treatments for RCDs.

The purpose of this retrospective study was to describe the demographic features, clinical follow-up and treatment of patients with RFD.

METHODS

Thirty-seven cases of RFD that were followed up and treated at our clinic between 2006 and 2019 were retrospectively analyzed. Information was obtained from the patients' files. Patient characteristics as well as family history, age at presentation, first bleeding symptoms and bleeding episodes, treatment of bleeding episodes, prophylactic treatments, and surgical approaches applied were recorded. The first coagulation screening tests were performed using prothrombin time (PT) and activated prothrombin time (aPTT). Specific factor deficiency and inhibitor levels were investigated for the cases according to the results of the PT or aPTT tests. FXIII levels were evaluated qualitatively by screening for the lysis of formed clots in 5 mol/L of urea without prolonged PT and aPTT in patients with hemorrhagic diathesis. Patients with factor activities lower than 50% were included in the study. Values under 100 mg/dL were defined as hypofibrinogenemia.

Statistical Analysis

Simple descriptive analyses, including mean, median, and range, were used to summarize the results using SPSS version 19 (SPSS Inc., Chicago, IL).

RESULTS

In this study, 64.8% of the patients were males and 35.2% were females. Patients' demographic characteristics and age at presentation are shown in Table 1. The distribution of RFD is shown in Figure 1. The most common factor deficiency was FVII deficiency (29.7%) (Figure 1). Parental consanguinity was found in 48.6% of cases. Parental consanguinity rates were 100% in fibrinogen deficiency and 66.6% in FXI deficiency. Factor levels were less than 5% in 18.7% of patients, 5%-30% in 43.7% of patients, and 30%-50% in 37.5% of patients. Factor levels were undetectable in five patients with FXIII deficiency. Fibrinogen levels of the hypofibrinogenemia patients were below 100 mg/dL (74 mg/dL in one, 50 mg/dL in one, and 40 mg/dL in three). FV and FVIII levels in a patient with combined FV and FVIII deficiency were 35% and 28.7%, respectively. Moderate FVII deficiency was determined in 18.9% of patients and mild deficiency in 10.8%. Moderate or severe factor X deficiency was determined in 10.8% of patients, and mild, moderate, or severe FXI deficiencies in 16.2%. Grade 1 bleeding symptoms (Bleeding that occurred after trauma or drug ingestion) were observed in 29.7% of symptomatic patients, grade 2 symptoms (Spontaneous minor bleeding: bruising, ecchymosis, minor wounds, oral cavity bleeding, epistaxis, and menorrhagia) in 13.5%, and grade 3 (Spontaneous major bleeding: hematomas, hemarthrosis, CNS, GI, and umbilical cord bleeding) in 56.7%. Life-threatening CNS bleeding was determined in four patients with RFD after trauma. Ecchymosis and epistaxis were most frequently detected in FVII deficiency at a level of 18.9%. The gastrointestinal system (GIS) bleeding rate was determined as 8.1% in fibrinogen and FV deficiencies. The type of bleeding at diagnosis and clinical findings are shown in Table 2, while the surgical procedures performed are shown in Table 3. Adenoidectomy was performed on 27% of patients with FVII deficiency. Circumcision was performed on 67% of patients with

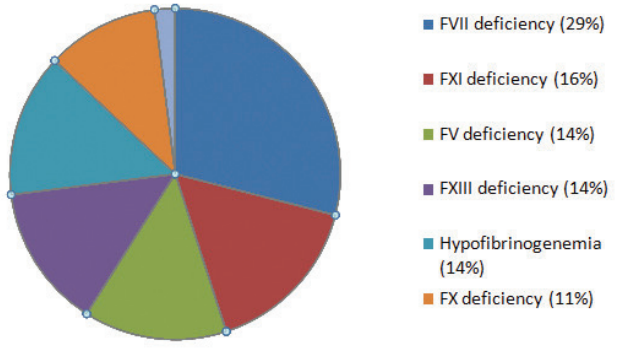

Figure 1. Distrubition of rare factor deficiencies

FXI deficiency, 27% of patients with FVII deficiency, and 20% of patients with FV deficiency. Fresh frozen plasma (FFP), fibrinogen concentrate, or rFVIIa in combination with tranexamic acid were administered before surgery. Tranexamic acid was initiated in patients who were to undergo circumsion, adenoidectomy, and undescended testis surgery and in those with mucosal bleeding, in three doses of 10 mg/kg/dose iv 8 h before surgery, and was maintained for two or three days after the surgery depending on bleeding status. Tranexamic acid was not used preoperatively in hematuria patients. No post-operative complications were observed.

DISCUSSION

Since most RFDs are inherited in an autosomal recessive manner, they are more prevalent in countries where consanguineous marriages are common. An autosomal dominant inheritance has been reported in some cases of FXI deficiency and dysfibrinogemia (2). Although there is no national record system in Turkey, Tugcu et al. (4) reported a consanguineous marriage rate of 49.5% in their study of 192 RFDs, similar to the rate of 48.6% in this study.

FVII deficiency has been reported as the most common RFD in studies from Iran, Italy, and North America, and was also the most common RFD in our study, with a rate of 29.7%. Sharma et al. (5)

Table 1. Patients' demographic characteristics

	Fibrinogen deficiency	FV deficiency	FV + FVIII deficiency	FVII deficiency	FX deficiency	FXI deficiency	FXIII deficiency	Total
Patients	5 (13.5%)	5 (13.5%)	1 (2.7%)	11 (29.7%)	4 (10.8%)	6 (16.2%)	5 (13.5%)	37
Sex								
Male	2	4	-	10	-	5	3	24 (64.8%)
Female	3	1	1	1	4	1	2	13 (35.2%)
First bleeding time								
<1 year	5	1	-	2	1	-	-	9 (24.3%)
1-5 year	-	-	-	2	3	3	5	13 (35.1%)
>5 year	-	4	1	7	-	3	-	15 (40.5%)
Consanguinity	5	1	1	4	2	4	1	18 (48.6%)
Factor activity							Factor activity can not be measured	
<5%	2	-	-	-	2	2		6
5%-30%	-	3	-	7	2	2		14
30%-50%	3	2	1	4	-	2		12
Clinical symptoms								
Grade 1	-	-	-	7	1	2	1	11 (29.7)
Grade 2	1	1	1	-	1	-	1	5 (13.5%)
Grade 3	4	4	-	4	2	4	3	21 (56.7%)
Asymptomatic	-	-	-	-	-	-	-	-
Prophylaxis	2	-	-	1	1	-	-	4 (10.8%)

Table 2. Patients' clinical manifestations

	Fibrinogen deficiency (N:3)	Fibrinogen + FXIII deficiency (N:2)	FV deficiency (N:5)	FV + FVIII deficiency (N:1)	FVII deficiency (N:11)	FX deficiency (N:4)	FXI deficiency (N:6)	FXIII deficiency (N:5)
Ecchymosis n (%)	2 (5.4)	2 (5.4)	1 (2.7)	1 (2.7)	3 (8.1)	2 (5.4)	2 (5.4)	2 (5.4)
Epistaxis n (%)	2 (5.4)	2 (5.4)	1 (2.7)	1 (2.7)	4 (10.8)	2 (5.4)	2 (5.4)	1 (2.7)
Umbilical bleeding n (%)	2 (5.4)	2 (5.4)	1 (2.7)	-	-	-	-	1 (2.7)
GİIS bleeding n (%)	1 (2.7)	1 (2.7)	1 (2.7)	-	-	-	-	-
Muscular hematoma n (%)	-	-	1 (2.7)	-	-	-	-	2 (5.4)
Joint bleeding n (%)	-	-	1 (2.7)	-	1 (2.7)	1 (2.7)	-	1 (2.7)
CNS bleeding n (%)	1 (2.7)	1 (2.7)		-	1 (2.7)	1 (2.7)	-	-

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

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Table 3. Surgical procedures performed

	Fibrinogen deficiency (N:5)	FV deficiency (N:5)	FVII deficiency (N:11)	FX deficienc (N:4)	FXI deficiency(N:6)
*Circumsion (n, %)	-	1 (20)	3 (27)	-	4 (67)
*Adenoidectomy (n, %)	-	-	3 (27)	-	-
*Undescended testis surgery (n, %)	-	-	1 (9)	-	-
*Humerus fracture surgery (n, %)	-	-	1 (9)	-	-
*ASD surgery (n, %)	1 (50)	-	-	-	-
*Mastoidectomy (n, %)	-	-	1 (9)	-	-
*Mass excision (n, %)	-	-	-	1 (25)	-
*İntracerebral hematoma evacuation, duraplasty (n, %)	-	-	-	1 (25)	-
*Developmental hip dysplasia surgery (n, %)	1 (50)	-	-	-	-

ASD: atrial septal defect, GIS: gastrointestinal system, N: total number of patients for each factor defiency, n: number of patients with the specific surgical method

reported FX deficiency as the most common RFD, while it was the fourth most common RFD in our study, with a rate of 10.8%.

Patients with RFD may present with a range of bleeding symptoms, from post-traumatic bleeding to severe attacks during or after birth. In some factor deficiencies, the factor level is directly related to the hemorrhagic risk, although this is not applicable in every case. The first correlation between factor level and bleeding severity in RFD was reported by the EN-RBD based on data from 489 patients in 13 treatment centers in Europe (6). Peyvandi et al. (6) found a strong correlation between bleeding severity and coagulation activity in fibrinogen, combined FV and FVIII, FX, and FXIII deficiencies, while a weak correlation was determined for FV and FVII deficiencies. No correlation was observed between factor level and bleeding severity for FXI deficiency. In the present study, the correlation between bleeding severity and factor level could not determine. The factor level was below 5% in two patients with FX deficiency. A life-threatening CNS bleeding was observed in one patient and intramuscular hematoma in the other. The factor level was between 30% and 50% in one patient with combined FV and FVIII deficiency, and no bleeding other than grade 1 bleeding was observed in this patient.

CNS bleeding was observed in one of the two patients with hypofibrinogenemia and pericardial tamponade in the other, despite the administration of fibrinogen concentrates and FFP before surgery.

Hemarthrosis and intramuscular bleeding are the most common symptoms in patients with hemophilia, while mucocutaneous bleeding is more common in RFDs (7). In our study, CNS, GIS, umbilical bleeding, hemarthrosis, and hematomas (grade 3 bleeding) were the most common bleeding symptoms (55.2%). RFDs are generally diagnosed after bleeding, and 40% of patients were diagnosed at an age >5 years.

Male children in various societies, including Turkey, have been circumcised for thousands of years for religious and cultural reasons. The known risk of circumcision in normal children is 0.2%-0.6%, but it constitutes a life-threatening risk in children with bleeding disorders (4). The families of children with bleeding disorders wish to see their children circumcised despite the known risks. This is an important ritual for most patients and their families, and is actually a social obligation for boys. As with other surgical procedures, appropriate precautions must be taken in children with bleeding disorders. Since there are few available studies on circumcision and surgery in RFD, the centers' clinical experiences are particularly important (8,9). In our study, patients received tranexamic acid 8 h prior to circumcision. While FFP was administered before surgery in cases of FV and FXI deficiency, it was maintained postoperatively depending on the bleeding status. rFVIIa was given to patients with FVII deficiency. Fibrinogen and FFP were administered before atrial septal defect surgery in fibrinogen deficiency, and combined coagulation concentrate (Cofact®) was administered before mastoidectomy in FX deficiency.

Little is known concerning prophylaxis in RFDs. This is only recommended for short-term use or after surgery. Tugcu et al. (4) applied prophylaxis in cases of fibrinogen, FVII, and FX deficiencies. Prophylaxis after severe, life-threatening bleeding reduces morbidity and mortality in RFDs. In our study, prophylaxis was applied to four patients with fibrinogen, FVII, and FX deficienc because of CNS bleeding. Care must be taken with prophylaxis in FX and fibrinogen deficiencies due to the risk of thrombosis.

RFDs can be detected through preoperative screening, clinical symptoms of bleeding, or incidentally. Clinical diagnosis is therefore difficult. There is no therapeutic strategy for RFDs. Investigation of cases in terms of diathesis before surgery and the management of life-threatening bleeding and surgeries are of vital importance.

We believe that the following procedures should be applied for the treatment and prophylaxis of RFDs and in preparation for surgery.

Tranexamic acid was initiated with three doses of 10 mg/kg/dose iv 8 hours before surgeries, such as circumcision, adenoidectomy, and tonsillectomy surgeries and mucosal bleedings, and was

maintained for two or three days after surgery depending on the bleeding status.

In fibrinogen deficiency, fibrinogen concentrate was given at a dosage of 30-40 µg/kg/dose, in patients with grade 2,3 bleedings, and half an hour before surgery. After one hour, the patient went for operation with a level of 200 mg/dL.

In FX deficiency, combined coagulation concentrate (Cofact®) was given at 50 units/kg/dose; in FVII deficiency, rFVIIa was given at 30 µg/kg/dose; and in FV, FXI, and FXIII deficiencies, FFP was given at 15 mL/kg/dose, half an hour before surgery. After one hour, the patient went for surgery with appropriate factor level. Factor therapy can be continued for 24-72 hours according to the patient's bleeding condition. Although prophylaxis is controversial in patients with CNS bleeding, our patients have been receiving prophylaxis for approximately 2 years. No complication or bleeding were observed in our patients and, due to this, we think that prophylaxis is appropriate after CNS bleeding.

Study Limitations

This study has some limitations. The longitudinal cohort had a small sample size, and genetic mutation analysis could not be done.

CONCLUSION

In summary, our results demonstrate that the most common RFD is FVII deficiency, followed by FXI deficiency in Turkish children. RFDs are more prevalent in Turkey than in Western countries due to the high parental consanguinity rates, indicating the need to raise public awareness on the risks of consanguineous marriages and to improve access to genetic counseling and testing facilities. Delayed diagnosis and the lack of prophylactic replacement therapy are the main risk factors that increase life-threatening bleedings. The need for a national bleeding disorders registry is indispensable for the collection of accurate data on the number of patients, complications, and treatment statistics in order to plan effective interventions that can improve the quality of care.

Ethics Committee Approval: Retrospective study.

Informed Consent: Written informed consent, approved by our institutional review board, was obtained from all patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - H.S.; Concept - N.E.; Design - E.E.; Data Collection and/or Processing - N.E.; Analysis and/or Interpretation - A.B.; Literature Search - N.E, A.B.; Writing Manuscript - N.E.

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