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Inherited Rare Factor Deficiencies: Single-centre Experience

Kalıtsal Nadir Faktör Eksiklikleri: Tek Merkez Deneyimi

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Abstract

Objective: Bleeding is one of the most important problems in humans. Absence, deficiency or dysfunctions of protein factors in the coagulation system can cause prolonged bleeding, morbidity or mortality. Although factor VIII, factor IX and von Willebrand factor deficiencies are the most common, deficiencies in all other factors exist, called rare factor deficiencies. This study aimed to present the clinical presentations, laboratory findings, treatments, and surgical interventions in patients with rare factor deficiencies other than factor VII followed up in our clinic.
Materials and Methods: Patients who were diagnosed with rare factor deficiency other than factor VII in the department of pediatric hematology and oncology between July 1997 and June 2020 were included in this study. Patients' demographic characteristics, clinical presentations, family history, prothrombin time, activated partial thromboplastin time and factor levels, treatments and surgical interventions were recorded retrospectively from patients' files.
Results: Nineteen patients were included in the study, of which 7 (37%) had factor X deficiency, 5 (25%) had factor XI, 3 (16%) had factor V+VIII, 2 (10%) had factor V and 1 (5%) had factor I and XIII deficiencies. Parents of 12 patients had consanguinity marriages. All patients with factor X deficiency had bleeding episodes, and three of them were under prophylaxis with prothrombin complex concentrate. Other patients were under on-demand treatment. In total, 19 surgical interventions (11 minor; 8 major) were performed.
Conclusion: Rare bleeding disorders are very uncommon and heterogeneous, with variable associations between coagulation factor activity and bleeding phenotype. A multidisciplinary and expertise team (haematologists, nurses, gynaecologists, obstetricians, orthopaedist, etc.) is necessary for the treatment and regular follow-up of patients with rare bleeding disorders.

Keywords
Rare factor deficiencies, clinic, treatment, surgery

Anahtar Kelimeler
Nadir faktör eksiklikleri, klinik, tedavi, cerrahi

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Öz

Amaç: Kanama insan hayatındaki en önemli sorunlardan bir tanesidir. Koagülasyon sisteminde yer alan faktörlerin eksikliği, yokluğu veya fonksiyon bozukluğu uzamış kanama, morbidite ve mortaliteye sebep olmaktadır. Faktör eksikliklerinin büyük çoğunluğu faktör VIII, faktör IX ve von Willebrand faktör eksikliği olup diğer faktör eksiklikleri nadir faktör eksiklikleri olarak adlandırılır. Bu çalışmada, nadir faktör eksikliği olan hastaların klinik özellikleri, laboratuvar bulguları, tedavileri ve uygulanan cerrahi girişimler sunulmuştur.
Gereç ve Yöntemler: Çocuk hematolojisi ve onkolojisi bilim dalında Temmuz 1997 ve Haziran 2020 tarihleri arasında takip edilen faktör VII eksikliği dışında nadir faktör eksikliği tanısı alan hastalar çalışmaya dahil edildi. Hastaların demografik özellikleri, klinik bulguları, aile hikayeleri, protrombin zamanı/aktive parsiyel

tromboplastin zamanı ve faktör düzeyleri ile tedavileri ve cerrahi girişimler hasta dosyalarından retrospektif olarak tarandı.
Bulgular: On dokuz hasta çalışmaya dahil edildi. Yedi hasta (%37) faktör X, 5'i (%25) faktör XI, 3'ü (%16) faktör V + faktör VIII, 2'si (%10) faktör V ve 1'er (%5) hasta faktör I ile faktör XIII eksikliği tanısı almıştı. On iki hastanın ebeveynlerinde akraba evliliği vardı. Faktör X eksikliği olan tüm hastaların kanama hikayesi olup 3 hasta protrombin kompleks konsantresi ile profilaksi tedavisi almakta ve diğer hastalar kanadıkça tedavi almaktaydı. Toplam 19 cerrahi girişim uygulanmış olup bunların 11'i minör, 8'i majör cerrahi girişimdi.
Sonuç: Nadir faktör eksiklikleri çok nadir hastalıklar grubundan olup değişik tablolarda karşımıza çıkmaktadırlar. Mevcut olan faktör düzeyi ve klinik arasında her zaman bir korelasyon bulunmamaktadır. Bu nedenle nadir faktör eksikliği olan hastalar multidisipliner (hematoloji, hemşire, jinekoloji, ortopedi...) ve deneyimli ekiplerin olduğu merkezlerde düzenli takip ve tedavi edilmelidir.

Introduction

Bleeding is one of the most important problem in human's life and the coagulation system, which is very complex plays a role to stop bleedings (1). Absence, deficiency or dysfunctions of factors which are the proteins in coagulation system can cause prolonged bleeding, morbidity or mortality (1). Although the majority of factor deficiencies consist of factor VIII (hemophilia A), factor IX (hemophilia B) and von Willebrand factor, all other factor deficiencies called as rare factor deficiencies. Inherited quantitative or qualitative deficiencies of coagulation factors such as factor I (fibrinogen-FI), factor II (FII), factor V (FV), combined FV and factor VIII (FVIII), factor VII (FVII), factor X (FX), factor XI (FXI), factor XIII (FXIII), and vitamin K-dependent clotting factors (FII, FVII, FIX, FX) called as rare bleeding disorders (RBDs) (2). The deficiency of any of the coagulation factors may result in a coagulopathy leading to bleeding episodes (3,4). Hemophilia A (FVIII) and B (FIX) and together with von Willebrand disease, they account for 95% to 97% of all coagulopathies (5,6), however RCDs are much less prevalent, ranging from case in 500,000 to 1 in 2 million in the general population and it could be vary by country (7). Prevalence of RBDs increases in regions with a high rate of consanguinity marriages (3, 4). The diagnosis of these disorders is challenged due to their rarity and clinical heterogeneity. Additionally, treatment guidelines of RBDs is challenging (3). In this study, we present the clinical presentations, laboratory findings, treatments, and surgical interventions in patients with RBDs other than FVII deficiency followed up in our clinic.

Materials and Methods

Patients who were diagnosed as having rare factor deficiency other than FVII in İstanbul University Oncology Institute, Department of Pediatric Hematology and Oncology between July 1997 and June 2020, were included in the study. Patients with FVII deficiency were excuded due to reported in another study (8). The patients' demographic characteristics, clinical presentations, family history, prothrombin time, activated partial thromboplastin time, and factor levels, and treatments and surgical interventions were recorded retrospectively from the patients' files. Clinical bleeding episodes were classified into four categories (Table 1) (2).

Surgical interventions were classified as major and minor surgical interventions. Orthopedic, cardiovascular, neurologic system interventions, and open abdominal surgery are major surgical interventions, whereas endoscopic procedures, biopsy procedures, and dental procedures are minor surgical interventions. Type of surgical intervention, treatment modality, and post-operative complications (bleeding, infection, mortality with rates higher than expected) were recorded. Formal statistical analysis were not performed due to the small sample size in the study.

The study was approved by İstanbul University Oncology Institute Local Academic Board (protocol

Table 1. Clinical bleeding severity in rare bleeding disorders

Bleeding severity	Definition
Asymptomatic	No bleeding episode
Grade I	Trauma or drug ingestion (antiplatelet or anticoagulant therapy) releated bleeding
Grade II	Minor bleedings; mucocutenous bleedings (bruising, ecchymosis, oral cavity bleeding, epistaxis, menorrhagia)
Grade III	Major bleedings; soft tissue hematoma, hemarthrosis, CNS, GI and umbilical cord bleeding

CNS: Central nervous system, GI: Gastrointestinal

no: 109419, date: 02.07.2020) and informed consent was obtained from parents or legal guardians before enrollment in the study.

Results

Nineteen patients were included in the study. Seven (37%) of 19 were FX deficiency, 5 (25%) were FXI, 3 (16%) were FV+FVIII, 2 (10%) were FV deficiencies and 1 (5%) of them FI and FXIII deficiencies. Twelve patient's parents had consanguinity marriages. The demographic characteristics and laboratory results of the study population are shown in Table 2**.**

All patients with FX deficiency had bleeding episodes that 4 had Grade II, 1 had Grade III bleeding episodes. Three of them (#10, #12 and #13) under

Table 2. Demographics, clinical and laboratuary findings in rare bleeding disorders

No (#)	Gender	Type of deficiency	Diagnosis age (years)	Current age (years)	Diagnosis age (years)	Family history/ consanguinity of parents	Clinical presentation	PT (s)	aPTT (s)	Factor level (%)
1	F	FI	1 month	9	1 month	Absent/present	Bleeding of blood-flow area	180	120	<15 mg/ dL*
2	F	FV	10	12	10	Absent/absent	None	14.3	40.4	24.7
3	M	FV	5 months	1,5	5 months	Absent/present	Epistaxis, gingivorragia	51	7	0.1401
4	M	FV+VIII	24	32	24	Present/present	Epistaxis	15.5	41.7	FV=16 FVIII=17
5	F	FV+VIII	35	43	35	Absent/absent	Epistaxis, gingivorragia, menorrhagia	21.9	73.9	FV=4 FVIII=14.7
6	M	FV+VIII	2	6	2	Absent/absent	Gingivorragia	23.6	70.8	FV=4.1 FVIII=3.2
7	F	FX	4	30	4	Present/present	Epistaxis, gingivorragia, menorrhagia	141.8	70.4	2
8	M	FX	2	8	2	Present/present	Epistaxis	20.5	47.3	12.1
9	M	FX	3	17	3	Present/present	Epistaxis, hematuria	17	48	7.4
10	M	FX	3 months	15	3 months	Present/present	CNS bleeding, GI bleeding	14.1	102	1
11	M	FX	4	5	4	Present/absent	Epistaxis	16.5	40.5	58
12	M	FX	3	12	3	Present/present	Epistaxis, gingivorragia	48	65	0.5
13	M	FX	3 months	Exitus	3 months	Present/present	Epistaxis	23.7	45.6	0.5
14	M	FXI	1 month	8	1 month	Present/absent	None	11.6	62	6
15	M	FXI	20	39	20	Present/present	Wound bleeding	11.8	56	0.9
16	F	FXI	19	30	19	Present/present	Prolonged bleeding, menorrhagia	14.7	70.2	3.38
17	M	FXI	1	3	1	Absent/absent	None	11.8	43.5	21
18	M	FXI	4	15	4	Absent/absent	Hemoptysis	13	44.5	22
19	M	FXIII	1	9	1	Present/present	Umblical cord bleeding, ecchymosis	13.3	34.4	1.11

CNS: Central nervous system, GI: Gastrointestinal, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, *Fibrinogen level mg/dL, F: Female, M: Male

prophylaxis with prothrombin complex concentrate (PCC). One (#10) had central nervous system (CNS) bleeding and others (#12 and #13) who were also brothers had uncontrolded epistaxis. Other patients were under on-demand treatment.

Totally, 19 surgical interventions were performed. Eleven of them minor and 8 were major. Hemostasis plan was prepared according to patient's factor level, bleeding tendency and type of operation (Table 3).

Discussion

RBDs are a heterogenous group of diseases that result from deficiencies of a coagulation proteins and affect both males and females and inherited as autosomal recessive. There is no clear consensus in terms of treatment due to rarity, in contrast to hemophilia. Factor concentrates are available for FI, FVII, FX, FXI, FXIII and most of them are plasma derived factor concentrates; recombinant factor concentrates are only avaible for FVII and FXIII (4). For other RBDs PCCs, fresh frozen plasma (FFP) and cryoprecipitate are the treatment choices (3,4,9).

Available information on the worldwide data of RBDs from World Federation of Haemophilia Global Survey showed that FVII and FXI deficiencies are the most common RBDs and followed by the deficiencies of fibrinogen, FV and FX, FXIII and more rare FII and combined FV + FVIII deficiencies (10). These results were similar with the report of European Network of RBDs (2). In the present study, most common deficiencies were FX and FXI followed by FV+FVIII, FV, FI and FXIII deficiencies.

Fibrinogen deficiency may be either quantitative or qualitative. However, the most common symptom of afibrinogenemia is mucocutaneous bleedings, soft tissue bleeding, joint bleeding and prolonged bleeding from the umbilical stump could be seen. Additionally, spontaneus CNS bleedings could be the cause of death (3,11). In the present cohort, 1 patient was recorded as afibrinogenemia and she was diagnosed after birth

Table 3. Surgical interventions in rare bleeding disorders

No	Type of deficiency	Age of surgical procedure (years)	Type of surgery	Treatment	Complication
4	FV+FVIII	29	Dental interventions	FFP+FVIII	None
		29	Total thyroidectomy		None
5	FV+FVIII	38	Dental interventions	FFP+FVIII	None
		43	Thyroid biopsy	FFP+FVIII	None
7	FX	24	Dental intervention	PCC	None
		28	C/S	PCC	None
		29	Dental interventions	PCC	None
		30	Dental interventions	PCC	None
8	FX	3	Eyelid cyst excision	PCC	None
10	FX FX	9	Tooth extraction	PCC	None
		10	Tooth extraction	PCC	None
11	FX	4	Circumcision	FFP	None
12	FX	6	Adenodectomy	PCC	None
		6	Tooth extraction	PCC	None
		9	Tooth extraction	PCC	None
13	FX	3	Congenital nevus excision-maling melanoma	PCC	None
15	FXI	38	Inguinal hernia operation	FFP	None
17	FXI	3	Adenodectomy	Tranexamic acid	None
18	FXI	8	Circumcision	Tranexamic acid	None

C/S: Cesarean/section, FFP: Fresh frozen plasma, PCC: Protrombin complex concentrate

due to bleeding from blood-flow areas. Additionally, she is still under prophylaxis by fibrinogen concentrate and had no major bleeding episode. The patients can suffer from pain of unknown origin in their limbs due to cystic intraosseous lesions (12).

Mucosal bleedings are the most common bleeding types of FV deficiency. Life-threatening bleedings such as CNS bleeding, gastrointestinal (GI) bleeding, hemarthrosis are rarely seen in FV deficiency (13). Several mutations including missense, nonsense, frameshift, and splice sitemutations have been reported for FV deficiency (14). Factor V deficiency of this cohort (Table 1, #3) had homozygous, missense mutation in *FV* gene [c.(6197G>A);(6197G>A) p.(Cys2066Tyr)] and had severe form with frequent nose and gum bleeding episodes. On the other hand, other patient (Table 1, #2) had mild type and had no bleeding episode.

Combined FV+FVIII deficiency, characterized by concomitantly low levels of the two coagulation factors and is associated with a mild bleeding to moderate bleeding tendency, being together does not increase the bleeding tendency (15,16). Additionally, other bleeding types include bleeding after surgery, dental extraction and trauma (16). Combined FV+FVIII deficiency is totally different from FV deficiency and FVIII deficiency that this disease should not be thought as the same disease. The treatment of FV and FVIII deficiency is usually on-demand and FFP together with FVIII concentrate is used accoding to plasma factor levels (3,4,16). In the present cohort, 3 patients were diagnosed with FV and FVIII deficiency and all had mild bleeding symptoms such as epistaxis, gum bleeding and menorrhagia same as described patients in the literature. Two patients had surgical interventions and had no complication after surgery. Two of them received FFP and FVIII concentrate according to their factor levels and bleeding phenotype.

Most common bleeding symptom is epistaxis in factor X deficiency and patients may present severe bleeding symptoms such as CNS, or GI bleeding and hemarthroses or hematomas. Additionally, menorrhagia is common symptom of women with FX deficiency (3,17,18). The majority of our cohort was FX deficiency and 6 of 7 patients had epistaxis and 1 women had menorrhagia. One severe FX deficiency patient (Table 1, #10) had intracranial hemorrhage and GI bleeding. Miscarriage, uterine bleeding, postpartum hemorrhage and preterm labor could be seen during pregnancy (19). In the present study, the patient (Table 2, #7) had miscarriage and had cesarean/section. For the treatment of bleeding episodes, surgery and prophylaxis of FX deficiency, plasma derived FX concentrate or plasma-derived products such as PCC that also contain other clotting factors could be used (3,17,20). All bleeding episodes and also surgical interventions were treated with PCC due to inavaibility of plasma derived FX concentrate in this study. The patient (Table 2, #13) who had congenital nevus diagnosed as malign melonoma had multiple surgical interventions of lesions and died due to progression of malignancy (21).

Bleeding phenotype is not correlated with plasma FXI level (22). Although, patients with the severe deficiency are at a higher risk of bleeding, they may remain asymptomatic and partial deficient patients may bleed after trauma or surgery (3,23). Antifibrinolytics, FFP and plasma-derived-FXI concentrate could be used for the treatment of FXI deficiency (3). In our patients, no major bleeding was recorded although low levels of FXI and 2 patients had surgical interventions with FFP or tranexamic acid due to inavaibility of FXI concentrate.

The first symptoms of FXIII deficiency are umbilical cord bleeding and soft tissue hematoma. Symptoms of FXIII deficiency range from life-threatening bleeding to mild forms of bleeding (24-27). Only 1 patient had FXIII deficiency in our study and his factor level was low and he had umblical cord bleeding in his history. Plasma-derived-FXIII concentrate has been shown to be safe and effective. Hovewer, FXIII concentrate is not available, cryoprecipitate should be preferred to FFP due to higher FXIII content as in our country (3,28).

Conclusion

RBDs are very rare and heterogeneous, with variable associations between coagulation factor activity and bleding phenotype. A multidisciplinary and expertise team (hematologists, nurses, gynecologists and obstetricians, orthopedics etc.) is necessary for the treatment and regular follow-up of the patients with RBDs.

Ethics

Ethics Committee Approval: The study was approved by İstanbul University Oncology Institute

Local Academic Board (protocol no: 109419, date: 02.07.2020).

Informed Consent: Informed consent was obtained from parents or legal guardians before enrollment in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.Z., B.K., Design: B.Z., B.K., Supervision: B.Z., B.K., Fundings: B.Z., B.K., Data Collection or Processing: B.Z., B.K., Analysis or Interpretation: B.Z., B.K., Literature Search: B.Z., B.K., Critical Review: B.Z., Writing: B.K.

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