Research Article

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Rare Coagulation Disorders: A Retrospective Analysis of 156 Patients in Turkey

Nadir Koagülasyon Bozuklukları: Türkiye'deki 156 Olgunun Retrospektif İncelenmesi

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Abstract

Objective: To retrospectively evaluate the clinical findings, laboratory data, management, and outcome in a group of Turkish children diagnosed with rare coagulation deficiencies (RCDs) between January 1999 and June 2009.

Material and Methods: The Turkish Society of Pediatric Hematology-Hemophilia-Thrombosis-Hemostasis subcommittee designed a Microsoft Excel-based questionnaire for standardized data collection and sent it to participating institutions.

Results: In total, 156 patients from 12 pediatric referral centers were included in the study. The cost common RCDs were as follows: FVII (n = 53 [34%]), FV (n = 24 [15.4%]), and FX (n = 23 [14.7%]) deficiency. The most common initial finding in the patients was epistaxis, followed by ecchymosis, and gingival bleeding.

Conclusion: Initial symptoms were mucosal bleeding, and fresh frozen plasma (FFP) and tranexamic acid were the most commonly used treatments. We think that prophylactic treatment used for hemophilia patients should be considered as an initial therapeutic option for patients with rare factor deficiencies and a severe clinical course, and for those with a factor deficiency that can lead to severe bleeding.

Key Words: Rare coagulation deficiencies, Clinical findings, Laboratory data

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Özet

Amaç: Türkiye'de son 10 yılda nadir koagülasyon eksikliği olan çocukların klinik bulguları, laboratuvar değerleri ve tedavilerini geriye yönelik olarak değerlendirdik.

Gereç ve Yöntemler: Türk Pediatrik Hematoloji Derneği, Tromboz-Hemostaz-Hemofili Alt Komitesi tarafından standardize edilmiş excel sorgulama dosyaları her merkeze gönderilerek yanıt veren merkezlerin verileri toplandı.

Bulgular: Oniki çocuk hematoloji merkezinden toplam 156 hasta bu çalışmaya alındı. Çalışmamızda en sık görülen nadir koagülasyon bozuklukları FVII (n: 53 olgu, %34), FV (n: 24 olgu, %15.4), FX (n: 23 olgu, %14.7) olarak dağılım gösterdi. Tüm nadir koagülasyon bozuklukları içinde en sık görülen başlangıç semptomları sırası ile burun kanaması, ekimoz ve diş eti kanamasıydı.

Sonuç: Mukozal kanamalar ilk semptomları oluştururken, halen en sık kullanılan tedavi seçenekleri ise taze donmuş plazma ve treneksamik asitti. Ağır klinik semptomları olan ve şiddetli kanamaya neden olabilecek nadir koagülasyon bozukluklarının erken dönemlerinde de hemofili hastalarında kullandığımız proflaktik tedavinin düşünülmesi gerektiğini öneriyoruz.

Anahtar Sözcükler: Nadir koagülasyon bozuklukları, Klinik ve laboratuvar veriler

Introduction

Rare coagulation deficiencies (RCDs) of childhood are commonly inherited in an autosomal recessive pattern, and include factor I (FI), FII, FV, FVII, FX, and FXIII deficiency [1,2]. RCDs, as the term implies, are rarely encountered. A prevalence as high as 1/20,000 was reported in populations with consanguineous marriage; however, the estimated prevalence of RCDs is 1/500,000-1/2,000,000 [1,2]. Although most RCD patients are asymptomatic, patients present with bruising, and mucosal and dermal bleeding, such as ecchymosis, epistaxis, gingival bleeding, and menorrhagia [1-5]. In addition, hemarthrosis, hematoma, and central nervous system bleeding may be seen [2,3]. The frequency and severity of bleeding in RCD patients vary, and are related to the type and level of factor deficiency. While intracerebral hemorrhagia may be mostly seen in FX and FXIII, afibrinogenemia, and FVII deficiency, musculoskeletal bleeding (hemarthrosis and hematoma) more frequently occurs in afibrinogenemia, and FX, FXI, and FXIII deficiency [2,6-8].

There are 2 treatment options for RCDs—on demand and prophylactic. On demand treatment is usually administered to RCD patients by hematologists because of the rare symptoms of bleeding, and generally includes fresh frozen plasma (FFP), epsilon-aminocaproic acid (EACA), tranexamic acid, cryoprecipitate, activated or non-activated prothrombin complex concentrates (aPCC and PCC, respectively), and recombinant factor VIIa [1-10]. Treatment strategies for RCDs are largely based on the severity and localization of bleeding. Interestingly, EACA or tranexamic acid treatment alone controlled the bleeding in almost 33% of patients with RCDs [1,2]. As such, the present study aimed to retrospectively evaluate the clinical findings, laboratory data, management, and outcome in 156 Turkish children diagnosed with RCDs during a 10-year period.

Material and Methods

We retrospectively analyzed initial clinical and laboratory findings, management, and outcome data for 156 children with RCDs obtained from 12 pediatric referral centers in Turkey. The Turkish Society of Pediatric Hematology Hemophilia - Thrombosis - Hemostasis subcommittee designed a Microsoft Excel-based questionnaire for standardized data collection and sent it to the participating institutions. Ethics Committee approved the study.

All children were diagnosed with an RCD between January 1999 and June 2009. RCDs were diagnosed based on bleeding history, and prolonged prothrombin time (PT) and/or activated partial thromboplastin time (APTT) and low coagulation factor level (FVII, FV, FX, FXIII, and FXI <40%, and FI <100 mg dL^{-1}) [1-4]. Unfortunately, genetic diagnosis could have been performed in very limited patients.

Patient age, medical history, clinical findings, laboratory data (factors levels), treatment, and prognosis were recorded. Demographic, laboratory, and clinical data were analyzed using descriptive statistics. Patients with the 3 most common RCDs were grouped, as follows, to compare their clinical and laboratory findings: group 1 (FVII deficiency), group 2 (FV deficiency), and group 3 (FX deficiency). Group results were compared using student's t test and the Mann-Whitney U test. The level of statistical significance was set at $P < 0.05$. Statistical analysis was performed using SPSS v.13.0.

Table 1: Detailed data of rare Coagulation Disorders

n=156	n (%)	Girl / Boy n, (%)	Age of at diagnosis, median range (months)	Most common bleeding focus	Parental consanguinity/ Positive history of family n, (%)	Common treatment choices (%)	Rate of ICH n, (%)	Prophy laxis n, (%)	Cause of excitus n, (%)
FVII deficiency	53 (34)	19(34,6) / 34(65,4)	72 0,1-180	Epistaxis, GB, echymosis	13 (24.5) / 11 (20.8)	FFP (20.8) rFVII (15.1)	7 (13,2)	1 (1,8)	ICH 2 (3,6)
FV deficiency	24 (15,4)	9(37,5) / 15(62,5)	30 0,1-120	GB, echymosis, epistaxis	6 (25) / 6 (25)	FFP (54.2)	4 (16,7)	2 (8,3)	-
FX deficiency	23 (14.7)	10(43,4) / 13(56,6)	9 0,1-180	Epistaxis, echymosis, hematom	6 (26) / 4 (17,3)	FFP (27.3) aPCC (13.6) FX (4.5)	4 (17,3)	4 (17,3)	ICH 1 (4,3)
FXIII deficiency	16 (10.3)	5 (31,2) / 11 (68,8)	12 0,1-204	GB, epistaxis, ICH	9 (56,2) / 5 (31,2)	FFP (71,4) Trenx (35.7)	4 (25)	2 (12,5)	-
FI deficiency	15 (9.6)	7(46,6) / 8(53,4)	1 0,03-144	Echymosis, bleeding after trau., ICH	11 (73,3) / 9 (60)	FFP (78,6) Tranx (50) Cryopres (35.7)	4 (26)	1 (6,6)	ICH and Traffic accident 2 (13)
FXI deficiency	13 (8.3)	8(61,5) / 5(38,5)	72 3-180	Hypermenorhea, GB, echymosis	2 (15,3) / 5 (38,4)	Tranx (23) aPCC (7)	-	-	-

***ICH**;intracranial haemorrhagia, Tranx;Tranexamic acid, **FFP**; fresh frozen plasma, **aPCC**; activated prothrombin complex concantrates, **rFVIIa**; activated recombinant factor VII, **Cryopres**; Cryopresipitate, **GB**; Gingival Bleeding*

Table 2: Comparison of the 3 Most Common RCDs (FVII, FV, and FX Deficiency)

	Group 1 n = 53 FVII Deficiency	Group 2 n = 24 FV Deficiency	Group 3 n = 23 FX Deficiency	1-2 P	I-3 P	2-3 P
Age at diagnosis (months)	72	30	9	0.01**	0.003**	AD
Ecchymosis (%)	20.8	33.3	50	NS	0.01**	NS
Hemarthrosis (%)	3.8	8.3	18.2	NS	0.03**	NS
Hematoma (%)	5.7	12.5	31.8	NS	0.002**	NS
Epistaxis (%)	26	33.3	50	NS	0.04**	NS
Subconjunctival bleeding (%)	1.9	0	13.6	NS	0.039**	NS
Family history (%)	21,2	26.1	22.7	NS	NS	NS
Consanguinity (%)	25	26.1	27.3	NS	NS	NS
On demand treatment with FFP (%)	20.8	54.2	27.3	0.003	NS	NS
Prophylaxis (%)	1.9	8.3	18.2	NS	0.01**	NS
Mortality (%)	3.8	0	6.7	NS	NS	NS

**NS: not significant; **P < 0.05: statistically significant.*

Results

The distribution of RCDs was as follows: FVII deficiency (n = 53 [34%]), FV deficiency (n = 24 [15.4%]), FX deficiency (n = 23 [14.7%]), FXIII deficiency (n = 16 [10.3%]), FI deficiency (n = 15 [9.6%]), FXI deficiency (n = 13 [8.3%]), FXII deficiency (n = 6 [3.8%]), plasminogen deficiency (n = 3 [1.9%]), and combined FV-VII deficiency (n = 3 [1.9%]). Among all the patients, the most common initial finding was epistaxis, followed by ecchymosis, and gingival bleeding.

FVII deficiency was the most common RCD (n = 53 [34%]). Median age at the time of diagnosis in the 53 patients (19 girls and 34 boys) with FVII deficiency was 72 months (range: 0.1-180 months). The most frequently observed bleeding symptoms were epistaxis, gingival bleeding, and ecchymosis, and the parental consanguinity and positive family history rates were 24.5% and 20.8%, respectively. Molecular diagnosis was performed in only 2 of the 156 patients. FFP and recombinant FVIIa (rFVIIa) were the most common treatment choices in the patients that received on demand treatment; only 1 patient received prophylactic treatment with recombinant FVIIa. The mortality rate was 3.8% (n = 2) and the cause of mortality was intracranial bleeding in both cases.

Median age at the time of diagnosis was significantly higher in group 1 (72 months) than in group 2 (30 months) and group 3 (9 months). In all, 11 of the 53 patients in group 1 were treated with FFP. Recombinant FVIIa was administered to only 8 of 53 patients Despite the development of intracranial bleeding in 7 patients and

Table 3: Distribution of Intracranial Bleeding

Deficient Factor	Intracranial Bleeding n (%)	Dead/Alive
FVII	7 (13%)	2/5
FI	4 (26%)	2/4
FV	4 (16%)	-/4
FX	4 (17%)	1/3
FXIII	4 (25%)	-/4
FXII	1 (16%) -	-/1 -
FXI	-	-
All patients	24	5/19
Exitus rate in ICC		%20.8

2 patients died prophylaxis was started to only 1 patient after intracranial bleeding. Patient characteristics according to the type of RCD (FVII, FV, FX, FI, FXIII, and FXI deficiency) is shown in Table 1. Comparison of the 3 most common RCDs (FVII, FV, and FX deficiency; groups 1, 2, and 3, respectively) is shown in Table 2 and the distribution of intracranial bleeding according to the type of RCD is shown in Table 3.

Discussion

Clinical manifestations of RCDs vary from mild to severe, depending on the type of and level of factor deficiency, and underlying molecular defects [1,2]. Bleeding in patients with RCDs is generally a rare occurrence. Moreover, primarily hematologists follow-up and treat RCD patients, the management of whom is difficult due to limited experience and lack of clear treatment guidelines. Although historically only tranexamic acid and FFP were treatment options available to hematologists, currently, plasma-derived factor concentrates and recombinant factor concentrates are also available [1,2,6-12].

In countries in which consanguineous marriage is common, such as Iran, Turkey, and India, the frequency of recessively inherited coagulation deficiencies is high and the frequency of inherited deficiencies of fibrinogen, prothrombin, FV, FVII, FV+FVIII, FX, and FXIII is 3-7-fold higher in Iran than in Italy and the UK, as reported by Peyvandi et al. [13], who also reported that FXI deficiency was more frequent in the UK than expected, probably because of its population of Ashkenazi Jews. In the present study FXI deficiency was the least common RCD, as in Iran [13]. Consistent with the literature, the most common initial finding in the present study's patients was epistaxis, followed by ecchymosis and gingival bleeding [1-4]; however, the high rate of intracranial bleeding in the patients with FI and FXIII deficiency (26% and 25%, respectively) and menorrhagia as the most frequent type of bleeding (38%) in the patients with FXI deficiency are quite remarkable findings.

The diagnosis of FVII deficiency is often made during childhood, but symptoms of bleeding begin during the neonatal period in those with severe deficiency [9,11-14]. Mucosal bleeding detected most frequently in our series were in accordance with the pattern reported for FVII deficiency as epistaxis and gingival bleedings. Median age at the time of diagnosis was significantly higher in group 1 than in group 3, probably due to factor levels. 20.8% of patients in the present study were treated with FFP; rFVIIa was used in a limited number of patients (15,1%). Despite the development of intracranial bleeding and death in seven patients, prophylaxis was initiated in only 1 patient. rFVIIa is recommended for the treatment of FVII deficiency, as the half-life of this factor is very short. Frequent use of FFP may create fluid overload; in an effort to avoid this, FFP may be administered less frequently than needed to provide adequate bleeding control. Although rFVIIa has been available in Turkey since 2003 the present results show that most of the hematologists at the institutions that participated in the study did not use this treatment option, which could have been due to its high cost. This result and very limited implementation of prophylaxis are the issues that should be thought on it.

Most patients with FV deficiency present with epistaxis and mucosal bleeding, usually diagnosed before the age of 6 years; however, patients as old as 62 years with intracranial bleeding have been reported [10,15,16]. In the present study's patients with FV deficiency mean age at the time of diagnosis was 3.5 years, and gingival and nose bleeding were the most common types of bleeding. As no recombinant or FV concentrate products are commercially unavailable, FFP or antifibrinolytic treatment was used in 50% of the present study's patients, as previously reported [2].

Menagatti et al. reported the most frequent symptom of bleeding in patients with FX deficiency is epistaxis [17], and Peyvandi et al. reported that central nervous system bleeding, hematoma, and hemarthrosis are common [2]. It is known that more serious symptoms of bleeding occur in patients with FX deficiency than in those with other rare factor deficiencies [2,5]. In the present study the most frequently encountered symptom of bleeding was epistaxis, followed by ecchymosis, and hemarthrosis. Mean age of the patients at the time of diagnosis was significantly lower in those with FVII deficiency than in the other patients. In accordance with the literature, intramuscular bleeding and hemarthrosis occurred more frequently in the patients with FX deficiency, as compared to those with other factor deficiencies, and significantly more frequent hematoma and hemarthrosis rates compared to FVII deficient group. We observed a significantly higher rate of subconjunctival bleeding, which is a rarely observed form of bleeding, in the patients with FX deficiency than in those with FVII deficiency. In addition, the rate of prophylactic treatment was significantly higher in the patients with FX deficiency than in those with FVII deficiency. High rate of prophylaxis in FX deficiency, diagnosed at young ages with serious bleeding symptoms, is a satisfactory and acceptable approach.

Anemia occurs in 19%-49% and erythrocyte transfusion is required by 10%-20% of patients with rare factor

deficiencies [1]. We did not make an inquiry for these parameters in our series. Despite the reports on post-circumcision bleeding in some series as the most frequent diagnostic finding in rare factor deficiencies it was not within the first three bleeding symptoms of our three groups (FVII, FV, FX deficiencies) [1]. Acharya et al. reported a central nervous system bleeding-related morbidity rate of 9%-22% in patients with RCDs [1].

In the present study 15% (24/156) of the patients had intracranial bleeding. Whereas intracranial bleeding was not observed in any of the patients with FXII deficiency, 26% (the highest rate) of those with FI deficiency had intracranial bleeding; despite this fact, FI concentrate was administered to only 3 patients while FFP (78%) and tranexamic acid were used more frequently as treatment options. The mortality rate due to intracranial bleeding in the present study was 3% (5/156)—2 of the patients that died had FVII deficiency, 2 had fibrinogen deficiency, and 1 had FX deficiency. Ten of the 19 patients that survived intracranial bleeding were using prophylaxis. Despite the intracranial bleeding, lack of prophylactic treatment including FFP in nearly half of the patients (9/19) makes us think that it is necessary to review our treatment options in these patients.

While bleeding is expected in patients with rare factor deficiencies, the development of thrombus is rarely observed [18]. In the present study 1 patient with FXIII deficiency was hospitalized with the presumptive diagnosis of intracranial bleeding, but was eventually diagnosed as sinovenous thrombosis. The patient was heterozygous for factor V Leiden mutation and was treated successfully with low molecular weight heparin [18]. Patients with both FV and FVIII deficiency are generally diagnosed with mild or moderate mucosal bleeding [2,19]. Additionally, patients diagnosed with post circumcision bleeding or menorrhagia have been reported [21,22]. Mucosal bleedings were predominant in our 3 cases with FV-FVIII combined deficiency.

A frequent finding in patients with plasminogen deficiency is conjunctivitis, which can involve the cornea [22,23]. A pseudomembrane may develop on the gums, ears, and the respiratory tract, in addition to the eyes, and hydrocephalus may accompany the clinical picture [22,23]. In accordance, the presenting complaint in 2 of the present study's patients was ligneous conjunctivitis, and their ophthalmologic findings recurred and persisted despite intermittent surgical treatment.

In conclusion, in the majority of patients with rare factor deficiencies the initial symptom was mucosal bleeding, and FFP and tranexamic acid were the most commonly used therapeutic options. Difficulty diagnosing these rare factor deficiencies, especially at the molecular level, is a major problem in Turkey. Genetic diagnosis was made in only 2 of the present study's patients (both treated at the same center) via correspondence with a center abroad. Thus, diagnosis of all the other patients was based on medical history, symptoms, and coagulation testing; therefore, nationally defining and determining the centers that could perform diagnosis of genetic studies on this issue and providing these centers with financial support seem to be the most probable resolution of this problem. Lack of specific treatment guidelines that are agreed upon by the centers is another problem. We observed that episodic treatment was initiated according to the presence of symptoms, whereas prophylaxis was used on a very limited basis even though specific recombinant products for treating the deficiencies were commercially available. We think that the prophylactic treatment we use for hemophilia patients should be considered as an initial therapeutic option for patients with rare factor deficiencies and a severe clinical course, and in those with factor deficiencies that can lead to severe bleeding.

Conflict of Interest Statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

References

1. Acharya SS, Coughlin A, Dimichele DM; North American Rare Bleeding Disorder Study Group: Rare Bleeding Disorder Registry: Deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. J Thromb Haemost 2004; 2: 248-256
2. Peyvandi F, Palla R, Menegatti M, Mannucci PM: Introduction. Rare bleeding disorders: General aspects of clinical features, diagnosis, and management. Semin Thromb Hemost 2009; 35: 349-355
3. Peyvandi F, Mannucci PM: Rare coagulation disorders. Thromb Haemost 1999; 82: 1207-1214
4. Bolton-Maggs PH, Perry DJ, Chalmers EA, Parapia LA, Wilde JT, Williams MD, Collins PW, Kitchen S, Dolan G, Mumford AD: The rare coagulation disorders-review with guidelines for management from the United Kingdom Haemophilia Centre Doctors Organisation. Haemophilia 2004; 10: 593-628

5. Şalcıoğlu Z, Sayılan Şen H, Aydoğan G, Akıcı F, Akçay A, Tuğcu D, Başlar Z: Rare factor deficiency; experience of 18 years. Journal of Turkish Pediatric Hematology 2008; 2: 33-38
6. Brown DL, Kouides PA: Diagnosis and treatment of inherited factor X deficiency. Haemophilia 2008; 14: 1176-1182
7. Hsieh L, Nugent D: Factor XIII deficiency. Haemophilia 2008; 14: 1190-1200
8. Acharya SS, Dimichele DM: Rare inherited disorders of fibrinogen. Haemophilia 2008; 14: 1151-1158
9. Herrmann FH, Wulff K, Auerswald G, Schulman S, Astermark J, Batorova A, Kreuz W, Pollmann H, Ruiz-Saez A, De Bosch N, Salazar-Sanchez L; Greifswald Factor FVII Deficiency Study Group: Factor VII deficiency: Clinical manifestation of 717 subjects from Europe and Latin America with mutations in the factor 7 gene. Haemophilia 2009; 15: 267-280
10. Huang JN, Koerper MA: Factor V deficiency: A concise review. Haemophilia 2008; 14: 1164-1169
11. Lapecorella M, Mariani G; International Registry on Congenital Factor VII Deficiency: Factor VII deficiency: Defining the clinical picture and optimizing therapeutic options. Haemophilia 2008; 14: 1170-1175
12. Castaman G: Propylaxis of bleeding episodes and surgical interventions in patients with rare inherited coagulation disorders. Blood Transfus 2008; 6: 39-44
13. Peyvandi F, Duga S, Akhavan S, Mannucci M: Rare coagulation deficiencies. Haemophilia 2002; 8: 308-321
14. Mariani G, Bernardi F: Factor VII Deficiency. Semin Thromb Hemost 2009; 35: 400-406
15. Yoneoka Y, Ozawa T, Saitoh A, Arai H: Emergency evacuation of expanding intracerebral haemorrhage in parahaemophilia (coagulation factor V deficiency). Acta Neurochir 1999; 141: 667-668
16. Totan M, Albayrak D: Intracranial haemorrhage due to factor V deficiency. Acta Paediatr 1999; 88: 342-343
17. Menegatti M, Peyvandi F: Factor X deficiency. Semin Thromb Hemost 2009; 35: 407-15
18. Akbalik M, Duru F, Fisgin T, Tasdemir HA, Incesu L, Albayrak D, Ozyurek E: Cerebral thrombosis associated with heterozygous factor V Leiden mutation and high lipoprotein(a) level in a girl with factor XIII deficiency. Blood Coagul Fibrinolysis 2007; 18: 371-374
19. Spreafico M, Peyvandi F: Combined FV and FVIII deficiency. Haemophilia 2008;14: 1201-1208
20. Mansouritorgabeh H, Rezaieyazdi Z, Pourfathollah AA, Rezai J, Esamaili H: Haemorrhagic symptoms in patients with combined factors V and VIII deficiency in north-eastern Iran. Haemophilia 2004; 10: 271-275
21. Peyvandi F, Tuddenham EG, Akhtari AM, Lak M, Mannucci PM: Bleeding symptoms in 27 Iranian patients with the combined deficiency of factor V and factor VIII. Br J Haematol 1998; 100: 773-776
22. Mehta R, Shapiro AD: Plasminogen deficiency. Haemophilia 2008; 14: 1261-1268
23. Schuster V, Seregard S: Ligneous conjunctivitis. Surv Ophthalmol 2003; 48: 369-388