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Review Article

Clinical Profile and Bleeding Outcome of Pediatric Rare Bleeding Disorders: The Royal Hospital's Experience, Oman

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Abstract

Introduction: Rare Bleeding Disorders (RBDs), a group of inherited coagulation factor deficiencies, are more common in areas with a high rate of consanguineous marriages. Data on the frequency and outcome of RBDs among children in Oman are limited.

Aim: This study evaluated the clinical profile and bleeding outcomes of paediatric RBDs at the Royal Hospital, the largest referring centre in Oman, from 2010 to 2020.

Methods: This retrospective descriptive cohort study includes all Omani children, less than 13 years of age, diagnosed with RBDs, and followed at the Royal Hospital. The patient's data was retrieved from the electronic chart system.

Results: Forty-one patients (24 males and 17 females) were included. Based on factor level at diagnosis, 34(83%) patients have factor VII deficiency, four (9.7%) patients have factor XIII deficiency, one (2.4%) patient has fibrinogen deficiency, and one patient (2.4%) has factor X deficiency. Four (9.4%) patients required blood transfusion for active bleeding, 15(36.6%) patients were treated on demand with tranexamic acid, and 3(7.3%) patients were on regular prophylaxis with tranexamic acid. The mean period of follow-up was 3.15 years. The majority (87.8%) of patients had no active bleeding, and only two (4.9%) patients developed severe bleeding. The mean annual bleeding rate outcome was 0.2, 0.5, and 7 for patients with FVII, FXIII, and FX, respectively.

Conclusions: Omani children with rare bleeding disorders are commonly diagnosed incidentally. They usually do not require active treatment because their bleeding outcome is favourable.

Keywords: Rare bleeding disorders; Bleeding; Coagulation factors; Paediatric; Oman

Introduction

Rare Bleeding Disorders (RBDs) are a group of inherited coagulation factor deficiencies, including fibrinogen, factor II (FII), FV, FVII, FX, FXI, and FXIII deficiency [1,2]. These autosomal recessive disorders represent 3-5% of all hereditary coagulation factor deficiencies. Globally, the incidence of isolated factor deficiencies (fibrinogen, FII, FV, FVII, FX, and FXIII) is around 1/1,000,000 in the general population. Severe FVII and FXI deficiencies are more prevalent (1/500,000), while severe FXIII deficiency is rarer (1:1-2,000,000) [3].

Prior to factor replacement therapy and other medical advances, life expectancy was reduced in individuals with severe RBDs and other hereditary bleeding disorders. Complications from bleeding disorders include a higher risk of intracranial haemorrhage, acquired viral infections, ischemic heart disease, renal failure, and high-risk surgical and dental procedures [4]. Since individuals with an RBD have varying levels of coagulation factor deficiency, and residual coagulant factor level does not always predict bleeding propensity, there is a wide range of clinical manifestations [1]. Patients with mild to moderate RBDs are often not diagnosed until they present with excessive bleeding during or after invasive surgery, such as circumcision, surgery, or dental work. Other non-surgical cases often present with excessive mucocutaneous bleeding [5].

Although RBDs are rare, these serious factor deficiencies are

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more common in regions such as the Middle East and Southern India, where consanguineous marriages are more frequent [6]. For example, Iran has the highest global incidence of FXIII deficiency [5]. While this increase represents a significant clinical problem, it also provides an opportunity for more effective studies and scientific collaboration among affected countries.

Inherited RBDs may not be identified until adulthood, depending upon the severity of bleeding and clinical history. A Pakistani population study noted that the median diagnosis age was 9 years 3 months in a study population of 774 patients [7]. Until recently, the clinical profiles of children with RBDs in Oman were not described [8]. The population in Oman has a high rate of consanguineous marriages, and RBDs among this population are mostly inherited, autosomal recessive disorders [9]. Young children are particularly susceptible to this group of disorders and demonstrate unique features, including: severe, atypical bleeding in some children with moderate phenotype hypofibrinogenemia (defined as fibrinogen levels of 0.1–1g/L); a poor association between coagulation factor activity level and clinical bleeding in FVII deficiency; and severe bleeding tendency despite moderate laboratory phenotype severity. Furthermore, clinical severity is associated with the laboratory phenotype in almost all FV deficient children [9]. However, previous research indicates that a region-wide registry is warranted to better identify the genotype-phenotype association, epidemiology, and treatment options for these rare, but serious RBDs in Oman linked to a high rate of consanguineous marriages.

This present study describes the clinical profile and bleeding outcomes of paediatric RBDs from 2010 to 2020 at the Royal Hospital, the largest referring centre in Oman.

Table 1: Patient characteristics and clinical diagnosis of children diagnosed with RBDs in Oman.

Variable	Statistics
Age (y)	4.63
Range (y)	0 – 12
Gender, No. (%)	
Male	24(58.5)
Female	17(41.5)
Nationality, No. (%)	41(100)
Presentation Site, No. (%)	
Muscle	1(2.4)
Mucocutaneous	13(31.7)
Organs	1(2.4)
Context, No. (%)	
Spontaneous	9(22.0)
Traumatic	3(7.3)
Incidental	22(53.7)
Family Screening	5(12.2)
Diagnosis, No. (%)	
Fibrinogen	1(2.4)
Factor VII	34(83)
Factor XIII	4(9.7)
Factor X	1(2.4)
Follow up duration (y)	3.15

Table 2: Bleeding outcome and treatment of Omani paediatric RBDs.

VARIABLE	STATISTICS
Initial Treatment, No. (%)	
FFP	3(7.3)
Cryoprecipitate	0(0)
Factor Concentrate	1(2.4)
Tranexamic Acid	3(7.3)
PRBC	4(9.8)
On Demand Treatment, No. (%)	
FFP	2 (4.9)
Cryoprecipitate	1 (2.4)
Factor Concentrate	9 (22.0)
Tranexamic Acid	15 (36.6)
PRBC	0 (0)
Prophylaxis, No. (%)	
FFP	0(0)
Cryoprecipitate	1(2.4)
Factor Concentrate	3(7.3)
Tranexamic Acid	3(7.3)
PRBC	0(0)
Annual Bleeding Rate, No. (%)	
0/Year	36(87.8)
1/Year	1(2.4)
2/Year	2(4.9)
4/Year	1(2.4)
7/Year	1(2.4)
Severe Bleeding, No. (%)	2(4.9)

*RBD: Rare Bleeding Disorder
*FFP Transfusion: Fresh Frozen Plasma
*PRBC Transfusion: Packed Red Blood Cell

Methods

Study Design and Protocol

This retrospective descriptive cohort study (SRC #4/2021) was approved by the Royal Hospital Scientific Research Committee. The inclusion criteria were Omani children less than 13 years of age who were diagnosed with a RBD between 2010 and 2020 and were being followed at the Royal Hospital. Patients may have been diagnosed at other medical institutions. However, they had to be followed at the Royal Hospital to be included in this study cohort. The patient's data was retrieved from the hospital's electronic chart system (AlShifa). The collected data included the patient's date of birth, gender, age at presentation, clinical profile, factor levels, treatment, complications, and mean Annual Bleeding Rate (ABR). One patient was excluded from the final analysis due to discontinuation of follow-ups at the Royal Hospital.

Statistical Analysis

Data were analysed with SPSS software, version 24.0 (SPSS, Inc, Chicago, Illinois). Data are presented as frequency and percentage for qualitative variables, and means and range for quantitative variables.

Results and Discussion

Clinical Profile of Omani Children Diagnosed with RBDs

This study included 41 patients who were being followed at the Royal Hospital in Oman between 2010 and 2020. The patient characteristics and clinical diagnosis are shown in Table

1. There were 24(58.5%) males and 17 (41.5%) females in the study population, all of whom were of Omani nationality. The age range of patients at diagnosis was zero years old (soon after birth) to 12 years of age, with a mean age of 4.63 years.

The most common presenting complaint was mucocutaneous bleeding, which occurred in 13(31.7%) patients. Systemic bleeding was observed in 1(2.4%) patient and muscular bleeding was also observed in 1(2.4%) patient. The presence of symptoms that led to diagnosis was primarily incidental, occurring pre-operatively based on bloodwork results for 22(53.7%) patients. These observations were followed by the occurrence of symptoms due to spontaneous and traumatic events in 9(22%) patients and 3(7.3%) patients, respectively. Family screening led to a diagnosis in 5(12.2%) patients and 1(2.4%) patient was diagnosed through genetic testing. Rare events that were associated with diagnosis include: post-snake bite in 1(2.4%) patient; tooth extraction in 1(2.4%) patient; and post-operative complications in 1(2.4%) patient. Symptom presentation and diagnosis were not associated with vaccination or circumcision.

Based on coagulation factor levels at diagnosis, the most common RBD in this cohort was FVII deficiency, with 24 (83%) out of 41 patients having this deficiency. This finding differs from the recent study conducted in Oman, in which FXI deficiency was the most common deficiency observed in the Omani cohort [8]. The other coagulation deficiencies (fibrinogen, FXIII, and FX) were rarely seen in this cohort (Table 1). FVII deficiency varies phenotypically, with some patients experiencing little to no bleeding despite very low FVII activity, while other patients with similar levels may experience frequent bleeding [10]. The majority of cases in this cohort were identified following incidental bloodwork, which may be the contributing factor for the higher incidence of FVII deficiency in this study.

Bleeding Outcome and Treatment of Omani Paediatric RBDs

The bleeding outcome of this cohort of Omani paediatric RBD patients was remarkably favourable, as described in Table 2. Eleven (26.8%) patients required treatment upon initial diagnosis, with packed red blood cell (PRBC) transfusion being the most common treatment (Table 2). Just over one-third of the paediatric cohort (15 out of 41; 36.6%) were treated on demand with tranexamic acid, with factor concentrate being the second most commonly used treatment. Few patients required prophylaxis treatment, but when needed, factor concentrate and tranexamic acid were the two most commonly prescribed treatments. Over the mean follow-up period of 3.15 years, the majority of the cohort (36 out of 41; 87.8%) had no active bleeding, and only two (4.9%) of the patients developed severe bleeding. The mean annual bleeding rate outcome was 0.2, 0.5, and 7 for patients with FVII, FXIII, and FX, respectively.

Since the symptoms and clinical manifestations of RBDs vary, it is beneficial for all paediatric providers to become familiar with the initial evaluation of these rare disorders [11]. As demonstrated by this cohort, most RBDs were discovered before surgery. Health practitioners with patients who have mild RBD symptoms need to exercise caution during any routine procedure, such as bloodwork and dental work [12]. Advances in medicine bring promise for people with RBDs, both in terms of diagnosis and treatment. In nations such as Oman that have higher than usual levels of RBDs due to consanguineous marriages, thromboelastography could be employed as part of routine paediatric visits to detect inherited bleeding disorders early on [13]. Additionally, patients with severe bleeding may benefit from the rapidly advancing gene therapy field [14].

Study Limitations

A small study population is an inherent problem when studying rare diseases. This cohort included 41 paediatric patients, which is a similar cohort size to other Middle Eastern studies of RBDs [4,5,15]. However, the mean follow-up time in this study was just over three years, which may be too short of a time to fully understand the annual bleeding rate and other clinical factors. Due to potential regional differences, a national multicentre collaboration would benefit the understanding and long-term follow-up of patients with RBDs in Oman.

Conclusions

The data from the current cohort of Omani children with RBS suggests that these conditions are commonly diagnosed with bloodwork prior to operations. The patients' RBDs do not usually require active treatment because their spontaneous bleeding and annual bleeding rate outcome are favourable. However, a novel finding was the higher incidence of FVII deficiency in children of Omani nationality, which differs from previous research that reports FXI deficiency as the most common deficiency in their Omani cohort [8]. This may indicate a developing trend among Omani children, given the high rate of consanguineous marriages in this region.

A limitation of this study was the small sample size from which data could be extrapolated. The findings do, however, emphasize the need for additional multicentre data collection of patients with RBDs for long-term monitoring. Findings from future studies might further elucidate the natural epidemiology, ideal screening methods, optimal therapeutic options, effective treatment approaches, and unidentified knowledge gaps regarding these disorders. Research at the molecular level that may facilitate carrier detection and direct preventative measures is also warranted.

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Conflict of Interest

The authors have no competing interests.

The authors have no conflicts of interest to declare.

The authors have no interests which might be perceived as posing a conflict or bias.

Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: HAH, AAR, AAA, and IAG. Data collection, analysis, and interpretation of results: HAH, AAR, AAA, and IAG. Draft manuscript preparation: MAS and IAG. All

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