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RARE BLEEDING DISORDERS: SPECTRUM OF DISEASE AND CLINICAL MANIFESTATIONS IN KING FAHAD ARMED FORCES HOSPITAL OF JEDDAH, SAUDI ARABIA

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ABSTRACT

Background: Rare bleeding disorders (RBDs) are heterogeneous disorders, mostly inherited in an autosomal recessive pattern. The clinical picture of RBDs is highly variable making diagnosis and best treatment quite challenging. Current treatment is based on both replacement therapy and non-trans fusional treatment. **Objectives:** In this study, we present prevalence, clinical presentation, and management of Saudi patients with RBDs at King Fahad Armed Forces Hospital (KFAFH), Jeddah, Saudi Arabia. The study findings will be useful to set up a database of these rare bleeding disorders in our institute, which will help clinicians in the early diagnosis and management. **Methods:** In this retrospective case review, detailed clinical information's was extracted from medical records in all patients who had rare clotting factor deficiency at (KFAFH) over the period of (2013-2020). **Results:** Among 1,581 patients with suspected coagulation disorders, 639 (40.41%) had a bleeding disorder. 103(16.11%) had a rare bleeding disorder; with a male-to-female ratio of 1.01. The median patient age was 5 years. The most common disorder was factor VII deficiency (50 patients, 48.5%). The most common clinical presentation was epistaxis in 15 (14.56%) and bruising in 13 (12.62%) patients.

KEYWORDS: Rare Bleeding Disorders, Factor Deficiency, Factor assay, Saudi Arabia, Inherited Bleeding Disorders.

INTRODUCTION

Rare bleeding disorders (RBDs) refer to a heterogeneous hereditary deficiency of fibrinogen, prothrombin factor II [FII]), factor V (FV), combined FV, and factor VIII (FVIII), factor VII (FVII), factor X (FX), factor XI (FXI), factor XIII (FXIII), dysfibrinogenemia, and vitamin K-dependent clotting factors. They are mostly inherited in an autosomal recessive manner with clinical manifestations ranging from mild to severe bleeding.[1-6]

The consequences of bleeding can be simple or catastrophic, resulting in significant morbidity and mortality. RBDs represent 3-5% of all inherited coagulation deficiencies with a prevalence in the general population varying between 1 in 500,000 to 1 in 2 million.[1-5]

There is a wide variation in the manifestations, but the most common symptoms of all RBDs are mucosal and post-invasive procedural bleeding. Sometimes, life-threatening bleeding such as central nervous system bleeding is seen with afibrinogenemia, FX, and FXIII.[9,10]

The treatment of RBDs is based on the replacement of the deficient factor and the use of adjunctive therapies when the bleeding is mild.[5,9] The approach to the treatment of bleeding episodes and invasive procedures should be individualized and depends on the severity, frequency, and procedure-related risk of bleeding.[8]

Despite the progress made in the past years, due to the rarity of these deficiencies, the actual management of the bleeding episodes and particularly the prophylactic treatment are not well established.[1]

A higher frequency of these disorders is seen in areas of high consanguineous marriages, and it is known that

consanguinity rates vary from country to country.[3,6] Saudi Arabia is one of the countries with the highest consanguinity rates and the overall rate of consanguineous marriages is 57.7%.[18] Therefore, we present here the pattern of these disorders seen in a large tertiary care referral hospital in Saudi Arabia.

This study was designed to provide descriptive and analytical data on these rare bleeding disorders in our institute. A retrospective chart review was conducted to study the pattern and the clinical presentations of these patients. In addition, the disease prevalence and the treatment provided to these patients was also reviewed.

MATERIAL AND METHODS

Patient inclusion: All patients aged one year or older, referred to the lab for rare clotting factor assays (FII, FV, FVII, FX, FXI, FXII, FXIII, and fibrinogen) as investigation of suspected rare bleeding disorder and found to have deficient factor from January 2013 to December 2020 were included in the study.

Patient Exclusions: Patients with hypofibrinogenemia were excluded because fibrinogen levels are usually requested with DIC, hemophilia, Platelet's function disorders, and acquired bleeding disorders.

MATERIAL AND METHOD

This single center, retrospective cross-sectional chart review study was conducted in the Department of medicine /hematology division, King Fahd Armed Forces hospital, Jeddah, Saudi Arabia, from January 2013 to December 2020. The study was approved by the institute's Ethical Review Committee. A total of 1,581 patient charts were reviewed in the study.

All patients who were referred to the lab for rare clotting factor assays (FII, FV, FVII, FX, FXI, FXII, and FXIII) as investigation of suspected rare bleeding disorder and found to have deficient factors from January 2013 to December 2020 were included in the study. However, patients who had hypofibrinogenemia, platelet function disorders, or any acquired coagulation disorder were excluded from the study. In addition, fibrinogen was excluded as low levels can be seen in DIC and over-requested.

A total of 1581 orders of rare clotting factor assay, 942 were excluded due to duplications, a total of 639 patients had one or more deficient factors. Those 639 were reviewed by four investigators and 507 were excluded because they had acquired bleeding disorder, hemophilia, Von Willebrand disease or they did not have factor deficiency. A total of 132 patients were interviewed by phone calls and their medical records were reviewed. A detailed history including past and present bleeding history, site(s) of bleeding, number of bleeding episodes, family history, consanguinity, treatment history, and history of transfusions were taken from patients by phone interview.

Medical records of these patients were retrospectively reviewed. Detailed clinical information and demographic details were extracted from medical records including age, sex, past and present bleeding history, site(s) of bleeding, number of bleeding episodes, family history, consanguinity, severity and history of transfusions were taken. Additionally, laboratory data including (complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (APTT), bleeding time (BT), renal function and liver function test), the severity of the deficiency were reviewed.

Bleeding episodes were categorized based on the type (hematomas, hemarthrosis, central nervous system bleeding, gastrointestinal bleeding, umbilical cord bleeding, bruising, ecchymosis, minor wounds, oral cavity bleeding, epistaxis, and menorrhagia) and the nature of the bleeding symptom (spontaneous or post traumatic).

Treatment details were recorded by reviewing the past medical record of the patient and the treatment the patient had received. Patients were categorized into those who received treatment on demand or those given prophylactic treatment and those who did not require any treatment.

After data collection was completed, it was reviewed by three independent reviewers. Twenty-nine patients were excluded (one due to Von Willebrand disease, seven due to Hemophilia, one due to hypofibrinogenemia, eleven due to acquired factor deficiency, and nine due to DIC). Finally, we ended up with 103 patients. (Figure 1)

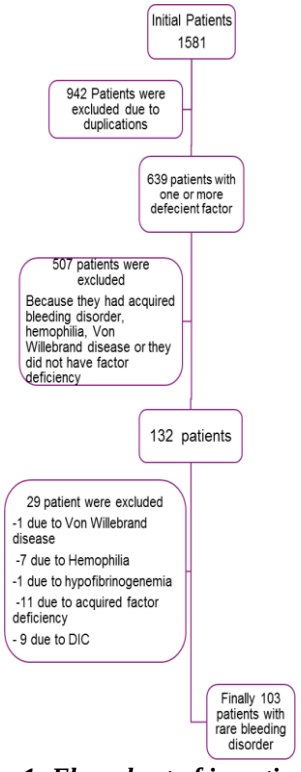

Figure 1: Flow chart of investigation.

RBD cases were diagnosed based on a coagulation profile and factor assays. Deficiency severity was defined based on the European Network of Rare Bleeding Disorders (EN-RBD).[8,11] *None of these patients had evidence of uremia, myeloproliferative disorders, acute leukemia, myelodysplastic syndrome, dysproteinemia, cardiopulmonary bypass, liver disease, or antiplatelet antibodies.*

The Coagulation assay was done on STA R MAX2 (STAGO) using company controls materials and reagents (STAGO-France). Initially, Prothrombin time (PT), activated partial thromboplastin time (APTT) were done to all suspected cases of bleeding tendencies then mixing study accordingly to differentiate factors deficiencies versus inhibitors.

Based on the results, specific factor assays were performed (PT-based factor assay was performed for factors V, VII, and X, while APTT-based factor assays were performed for factors VIII, IX, XI, and XII) using STAGO factor deficient plasma for both. Reference values for PT were 12-14 sec, APTT was 29-40 sec, and factor assays were 60-150 % for all factors except FXIII as per the manufacturer's instruction. Factor XIII level is based on the clotting method assays and it takes part in the final stages of the coagulation cascade by stabilizing the fibrin clot by polymerizing fibrin monomers. The reference range is 59-181% as per the manufacturer's instruction.

Complete blood count (CBC) was done on Anility HQ (Abbott analyzer) by using spectrophotometric and Flow cytometry methods. Tests for each sample were repeated to confirm factor deficiency. Patients with factor V deficiency were also checked for combined factor V and factor VIII deficiency by factor VIII assay.

Categorical variables were expressed as frequency and percentage, while quantitative variables were expressed as mean and standard deviation (mean ±SD). The baseline characteristics were compared using the chi-square test. All P-values were two-sided. $P<0.05$ was indicating statistical significance.

RESULTS

A total of 1,581 patients who were referred to our lab for rare clotting factor assays (FII, FV, FVII, FX, FXI, FXII, FXIII and fibrinogen) as investigation of suspected rare bleeding disorder were enrolled in our study. Among them, 639 (40.41%) were diagnosed with bleeding disorder. Out of the 639 patients, 103 (16.11%) were diagnosed to have a rare bleeding disorder (Table 1)

Table 1: Distribution of patients with RBD.

Inherited bleeding disorder	No. of patients, n (%) N=103
Factor II	0
Factor V	6 (5.82)
Factor VII	50 (48.5)
Factor X	14 (13.59)
Factor XI	4 (3.88)
Factor XII	20 (19.1)
Factor XIII	9 (8.73)
Combined Factor V+VIII	0

The distribution of patients according to different age groups presented in (Figure 2)

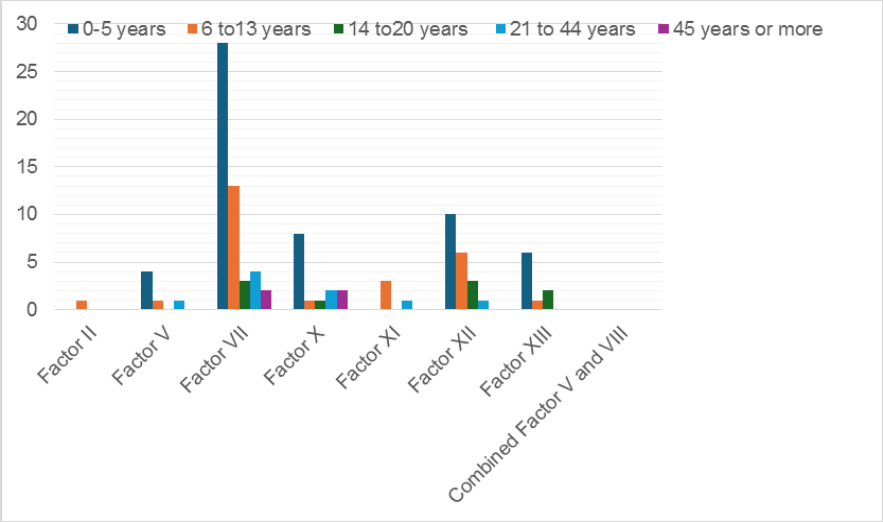

Figure 2: The distribution of patient according to age groups, total no. 103 patients with rare bleeding disorder.

Out of 103 patients diagnosed with a rare bleeding disorder, 52 patients were male (50.48%) and 51 patients were female (49.51%). The median age at diagnosis was 5 years with range between 1 day and 68 years, in addition to this most of our population was discovered incidentally, with only twenty-four patients (23.30%) presented with bleeding. The most common deficient factor was factor VII (50 patients, 48.5%), followed by factor XII deficiency (20 patients, 19.1%), factor X deficiency (14 patients, 13.59%), factor XIII deficiency in (9 patients, 8.73%), factor V deficiency (6 patients, 5.82%), and factor XI deficiency (4 patients, 3.88%). (Table 2).

Table 2: Frequency distribution and features of patients with rare bleeding disorders.)

Inherited bleeding disorder (N=103)	No, (%)	Median Age (yrs.)	Male (N)	Female (N)	Median Factor level (iu/ml)	Disease severity		
						Mild	Mod	Sever
Factor II	0 (0)							
Factor V	6(5.82)	3	3	3	0.36	≥0·1 iu/ml 4	<0·1 iu/ml 2	Undetectable 0
Factor VII	50(48.5)	5.98	28	22	0.32	>0·2 iu/ml 30	0·1–0·2 iu/ml 3	<0·1 iu/ml 15
Factor X	14(13.59)	5	5	9	0.32	>0·4 iu/ml 4	0·1–0·4 iu/ml 5	<0·1 iu/ml 4
Factor XI	4(3.88)	7	3	1	0.32	-	-	-
Factor XII	20((19.1)	5	11	9	0.44	-	-	-
Factor XIII	9(8.73)	1	3	6	0.43	≥0·3 iu/ml 5	0·3 iu/ml 2	Undetectable 2
Combined Factor V+VIII	0							

Consanguinity was found in 52 (50.48 %) of patients and family history of bleeding was found in twenty-seven patient (26.21%).

It was noted that most of the factor deficiencies ranged from mild to moderate 46 patients (44.6%), 12 patients (11.65%) respectively and only 21 patients (20.38%) were considered severe based on laboratory level.

Most of the patients were asymptomatic (68 patients, 66.01%) and the most common clinical presentation was epistaxis in 15 patients (14.56%) and bruising in 13 (12.62%) patients, gum bleeding in seven patients (6.79%), hematoma in four patients (3.88%), menorrhagia in three patients (3.88%), post-circumcision bleed in two patients (1.94%), post-operative bleed in two patients (1.94%), one patient has post-partum bleed (0.97%), and one has umbilical stump bleed (0.97%). Clinical features of patients with rare bleeding disorder are shown in (Figure 3)

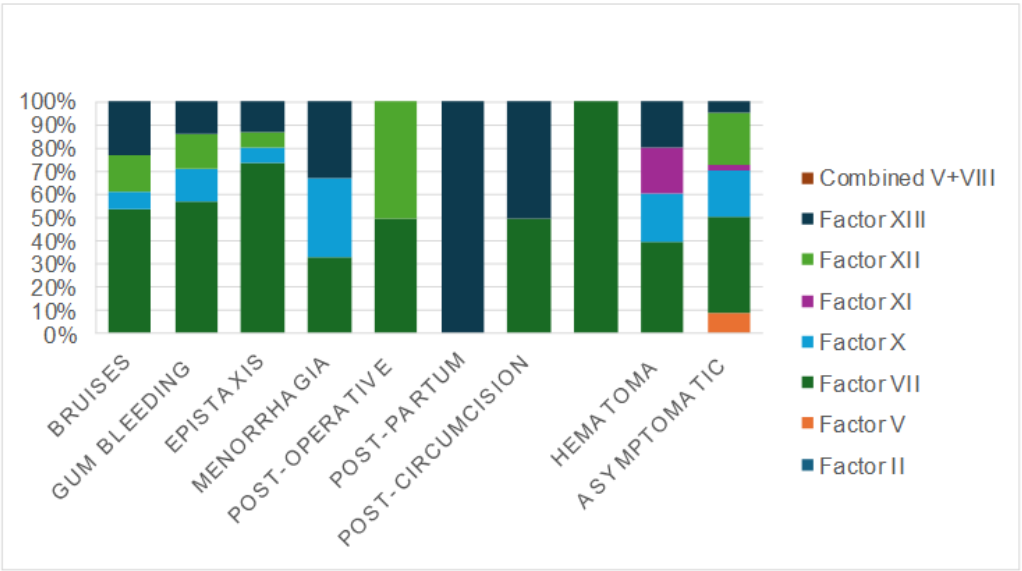

Figure 3: Clinical feature of patients with rare bleeding disorders.

Ninety-four patients (91.26%) did not require any treatment, while five patients (4.85%) were on prophylaxis and four patients (3.88%) received treatment on demand.

DISCUSSION

The prevalence of rare bleeding disorder and its management is known in developed countries, but still, there is a significant gap in knowledge of its prevalence in developing countries, especially in Arab countries.[3]

Studying our population and seeking to set up a database is an essential step for health planning programs and developing clinical treatment guidelines according to our resources and population.

In this study, the frequency of rare bleeding disorders was 16. 11% and the most common rare bleeding in our institute was factor VII deficiency (50 patients, 48.54%), followed by factor XII deficiency (20 patients, 19.41%) and factor X deficiency (14 patients, 13.59%), whereas several previous studies from southern Pakistan reported the frequency of rare bleeding disorders as 21.3% and FVII deficiency as the most common one[12], in India FX deficiency was the commonest[13,15], afibrinogenemia and factor VII deficiency were common in Egypt and Brazil, respectively[3,16,17] and in Iran reported the frequency of 15.6% and combined FV and VIII deficiency as the commonest (16%).[14]

In the current study, majority of patients did not develop complications except one patient developed intracranial bleeding, another developed gastrointestinal bleeding and two others developed musculoskeletal bleeding. Intracranial bleeding was seen in a patient with factor XIII deficiency, gastrointestinal bleeding with factor V deficiency, and musculoskeletal bleeding with factor X and factor XIII deficiency. However, Mahmood R et al.[3] reported factor X deficiency as the most common cause of intracranial bleeding, while Sharma SK et al.[15] shows factor XIII deficiency was the most common in an Indian study.

In comparison with a national data, there is a national survey among young adults in Saudi Arabia that revealed deficiencies in coagulation factors F-VIII in 14 (7.4%), F-IX in 15 (7.6%), F-II in two (3.3%), F-V in 17 (26.1%), FVII in two (3.1%), and F-X in one (1.8%) of study subjects.[7] Comparison of current study to the international data, shown in (Figure 4).[17]

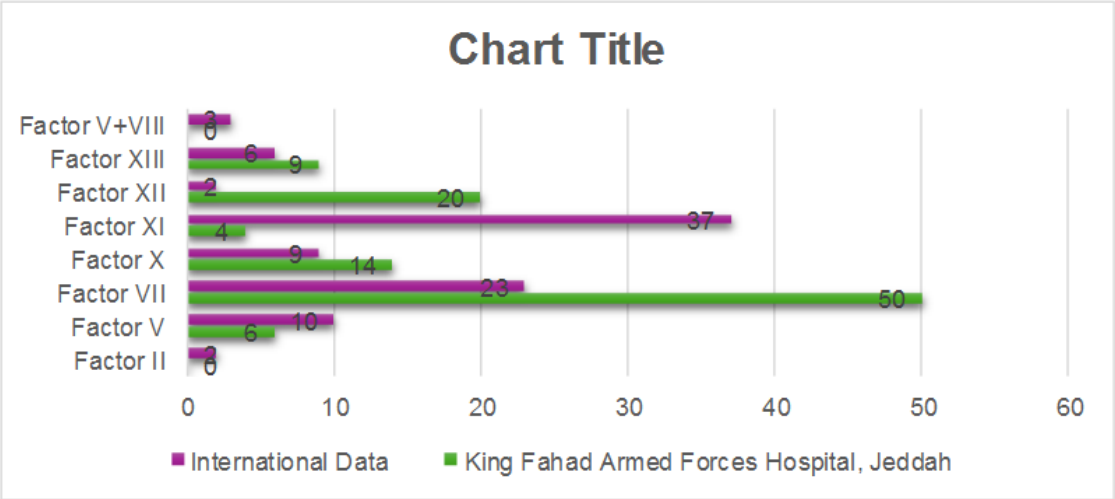

Figure 4: Comparison between current study and international data in patients with rare bleeding disorders There are several limitations to our study which include that the diagnosis of rare blood disease (RBD) was based on coagulation test results only, without further genetic studies, as this facility is not available in our institute.

In addition, one of the difficulties faced during data collection was the lack of details on the setting of diagnosis, severity of clinical manifestations and treatment details for which we relied mainly on the patient's medical records and phone call which itself was one of difficulties as they at times needed to be call more than once. Treatment details including transfusion and factor concentrate use was also missing, lack of electronic medical files, and the data were entered manually in medical files specifically clinical manifestations and presentation. Indeed, these difficulties are gradually being sorted out by the introduction of electronic laboratory and medical record facility which will help us in future research.

We tried intensively to cover the demographics, clinical presentations, disease severity, and different treatments received. However, our study included only patients referred to our lab for rare clotting factor assay, therefore it is possible that the prevalence and frequency of the rare bleeding disorders in our population may be much higher than what we reported.

Our hospital is part of medical services provided to military personnel and their families (parents, spouse and

children). The number of opened files in our hospital is 750,000 files which reflect a representative sample of general population where we can estimate the prevalence of the diseases.

Overall, the prevalence of rare bleeding disorder was 0.014% and the prevalence for each factor as follow factor II 0.001%, factor VII 0.007%, factor X 0.002, factor XI 0.0005, factor XIII 0.0012%.

However, future studies on large-scale Saudi populations are required including genetic phenotypes and patterns of disease. We hoped that this study will enhance more studies aiming to set up a standard guideline for early detection and management of rare bleeding disorders in our country in addition to setting up a national registry for the bleeding disorders.

According to the International Rare Bleeding Disorders Database, the frequency of these disorders increased 10-20 times where consanguinity is common such as Middle East countries and this was found in 51 (49.51%) patient of our rare bleeding disorders population.

CONCLUSIONS

The result of our study shows that the most common rare bleeding disorder in our population is factor VII deficiency, and the prevalence of these bleeding disorders is high in our population possibly due to a high number of consanguineous marriages. This suggest that we need further studies and a proper system for data collection.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived.

AUTHOR CONTRIBUTIONS

Alia A. Abotaleb conceptualized the manuscript, reviewed the literature, contributed in data analysis and interpretation, and wrote the first draft and finalized the final draft of the manuscript. Abdulrahim M. Basendwah contributed in data analysis, reviewed and critically edited the manuscript. Iman A. Alhazmi reviewed the the manuscript. Samy M. Attalah provided study raw data, reviewed, and edited the manuscript. Ehab M. Taha and Shabana A. Kamal reviewed the data. Maha M. Alshareef, Duaa A. Khan, Sumaia A. Felimban, Bushra Al Qadi, and Naif Aljohani collected and assembled the data. Samah A. Mokhlis provided the laboratory materials. All author approved the final manuscript draft and are accountable for all aspects of the work.

ETHICS MATTERS

This study was approved by the medical ethics committee.

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