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Research Article

Bleeding in Children with Inherited Factor Deficiency: Our Single-Center Experience in Jordan

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Abstract

Diagnosis and treatment of inherited bleeding disorders in children secondary to a deficiency in single or multiple coagulation factors are of great importance and represent a challenging issue in developing countries like Jordan.

The prevalence of bleeding disorders varies in different countries and their ethnic groups, and still, we have a shortage of documentation of these disorders related to diagnostic labs, variability of clinical presentation, family history of similar bleeding tendencies with some denial and ignorance about the seriousness and importance of early detection to prevent major bleeding conditions. Inherited factor deficiency (IFD) refers to Bleeding disorders that occur when one or more factors are missing or decreased from the blood, preventing normal blood clotting formation. Inherited means that the person was born with the deficiency and will have it for the rest of his or her life. They may also pass it on to their offspring.

The result of 80 patients with inherited factor deficiency who were diagnosed and followed at Queen Rania AL-Abdullah children hospital in the Pediatric Hematology department in the period between 2015 and 2021, were retrospectively studied regarding the frequency, diagnostic test, presentation, and management plan. Of these (80) patients, the majority of patients 42 (52.5%) were hemophilia A, 4 (5%) were hemophilia B, 6 (7.5%) were von Willebrand disease (vWD), and the remaining 28 (35%) were rare bleeding disorders.

The median age of the patients at the time of diagnosis was 3.5 years.

Thirteen patients (16.25%) present with major bleeding, 56 (70%) with mild to moderate bleeding and 11 patients (13.75 %) were asymptomatic, 38 (47.5%) of them were diagnosed with similar family history,27 (33.75%) are from consanguineous parents, and those who are asymptomatic they came either due to family history 2 (18.2%) or incidentally founded during the preoperative screening 9(81.8%). 63(78.75%) of patients are males and 17(21.25%) of them are females.

Treatment principles for bleeding or pre-operative preparation in these clotting factor deficiencies are based on what is deficient and replacement of it to achieve the hemostatic level required to form a clot and maintain it stable, we have either specific factor concentrate like factor VIII in hemophilia A, Prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) and cryoprecipitate (CRYO).

Patients with hemophilia A or B, factor 7 deficiency given the factor concentrate, patients with factor X deficiency and vitamin k dependent factor deficiency given the PCC complex, and patients with VWD unfortunately still we don't have the factor concentrate in our department waiting to be available for those patients in the coming period, and finally the remaining rare factor deficiency like factor XIII, factor V and fibrinogen we use FFP or CRYO.

In this study, we are going to present the prevalence, diagnostic approach, follow-up, and treatment modality of various bleeding histories, preoperative preparation, and the challenges we face.

Conclusion:

The variety in the clinical presentation of IFD leads to significant diagnostic and therapeutic challenges, sharing our experience in treating patients with inherited factor deficiency will help to improve diagnosis and management of these bleeding disorders, especially in countries with limited resources and facilities.

Key words: *Inherited factor deficiencies, prophylaxis, treatment, bleeding disorders.*

Introduction

Bleeding disorders in children are wide spectrum including inherited and acquired factor deficiency, platelet disorders, and VWD.

When we talk about inherited factor deficiencies: we mean congenital (inherited) bleeding disorders occur when one or more factors are missing or decreased from the blood, preventing normal blood clot formation, this means we have no cure for these disorders and they might be transmitted through generations. (1)

Among these disorders in coagulation we have VWD as the most common inherited coagulation abnormality followed by hemophilia A and B, and finally, what is called rare inherited factor deficiency (RIFD) refers to hereditary deficiencies of fibrinogen, prothrombin (factor II), FV, FVII, FVIII+FV, FX, FXI, and FXIII as well as disorders of fibrinolysis. (2) Rare inherited bleeding disorders are generally inherited as autosomal recessive disorders, except for dysfibrinogenemia and some cases of FXI deficiency, which can be autosomal dominant. (3)

The incidence of RIFDs is reported to be higher, particularly in countries where consanguineous marriages are common, like in Jordan and surrounding countries, in comparison to developed countries. According to World Bleeding Disorder Registry (WBDR) in 2019 there are global federations and organizations for hemophilia patients with consensus guidelines and organizations to support the diagnosis, management, and care of hemophilia patients. (4)

Unlike hemophilia, knowledge about RIFDs and their treatment guidelines is insufficient because they are rarely seen and have variable presentations, sometimes we don't have a clear family history of bleeding disorder as they pass it normally within the family or they deny mentioning their family history, especially in our societies, this leads to more delayed presentation till major and serious bleeding complications happen. (5)

Here in Jordan still we have some struggles regarding late presentation, delayed visits to the health care facility, and the registry of these cases which need a good database with a global effort from the health care providers in all sites for referral to more specialized centers for further evaluation, diagnose, and management.

We will present our experience at Queen Rania Children's Hospital (QRCH) in the diagnosis and treatment of patients with bleeding secondary to the factor deficiency to share with others and to help in building more collaborations to make guidelines, especially for the rare types of bleeding.

Methods

A retrospective chart review during the period from 2015 to 2021, our data were collected from the electronic files of the patient and the registered cases in our hematology clinic at QRCH, a total of (80) cases either diagnosed at the hematology department or referred from other hospitals were included in our study, noting that QRCH is a tertiary pediatric hospital with most of the bleeding disorders referred to our clinic.

The investigations of the patient with bleeding disorders done in specialized hematology and coagulation lab included CBC (complete blood count, bleeding time, prothrombin time (PT), partial thromboplastin time (PTT) and (international normalized ratio) INR, fibrinogen level blood film, vWD: Ag level and factor assay. If needed inhibitor assay can also be done.

Hope to add genetic tests for molecular characterization, carrier detection, and prenatal diagnosis in the coming years.

Regarding hemophilia patients, the diagnosis and stratification were done according to factor percentage into Mild, moderate, and severe cases of hemophilia A or B, if the level from (5%-40%), (1%-<5%) and (<1%) respectively. Our hematology lab used a one-stage coagulometric method to measure the factor assay and the precise level from 1% to 100% of the normal.

The correlation between the factor activity level and degree of bleeding differs from strong and predictable (for a patient diagnosed with a fibrinogen deficiency, FV+FVIII, FX, or FXIII) to no correlation for patients with FXI deficiency and this was reported in a multicenter cohort study by the European network of rare bleeding disorder (EN-RBD) among 489 patients.[6] but overall, major bleeding with life-threatening episodes like intracranial bleeding and hemarthrosis or spontaneous hemorrhages in muscles occur less frequently when compared to a patient with hemophilia.[7]

In a patient with suspected vWDs, we analyze von Willebrand antigen level (VWF: Ag), to stratify patients into typ1, type 2, and type 3. The ristocetin-induced platelet aggregation and the vWF: ristocetin cofactor (RCoF)assay are done once needed in our lab.

The bleeding history and treatment plan were collected from the patient file, special questionnaires were given to collect data from parents regarding the bleeding history, family history, use of at-home therapy or prophylaxis treatment, and several bleeds were also documented.

Patients' degrees of clinical bleeding were categorized into (asymptomatic and grade 1, 2, or 3 bleeding). This bleeding severity scale uses the most severe bleeding a patient has ever had. Grade I refer to induced bleeding episodes, Grade II refers to spontaneous minor bleeding episodes (eg, bruising, ecchymosis), and Grade III refers to spontaneous major bleeding episodes (eg, cerebral bleeds, gastrointestinal hemorrhage, or hemarthrosis) that require hospitalization. This classification is recommended by the European Network of rare bleeding disorders group. [8]

In our hospital treatment with the use of available factor concentrate for specific factor deficiency, like factor VIII, factor VII, and factor IX concentrate, PCC complex in patients with factor X deficiency

FFP or cryoprecipitate in treating other factor deficiencies like factor V, VWD, fibrinogen disorders, and factor XIII deficiencies.

Results

A total of (80) were studied, 63(78.75 %) of the patients were males and 17 (21.25 %) were females, the median age at the time of diagnosis was (3.5 years). Patients with hemophilia A constitute about 42 (50%), hemophilia B 4 (5%), VWD 6 (7.5%), and the remaining we consider them as rare bleeding disorders constitute 28 (35%): factor VII deficiency was 13 (46.4%) of patients, FX deficiency 5 (17.9 %), fibrinogen deficiency 3 (10.7%), factor V deficiency 2 (7.1%) factor XIII deficiency 2 (7.1%), 3(10.7%) cases were factor XI deficiency, and finally factor II deficiency no diagnosed cases in that period. (Figure 1.1, 1.2)

Factor levels were classified in hemophilia patients as severe factor deficiency <1% seen in 30 (65.2%) of patients, moderate factor level deficiency (from 1%-5%) in 14 (30.4%) of patients, and finally mild factor deficiency with factor level from (>5%-40%) seen in about 2 (4.4%) of patients. (Table 1.1)

Consanguinity rates for hemophilia patients were 11 (23.9%) and 3 (50%) for VWD, and 13 (46.4%) for rare bleeding disorders.

The prevalence rate of bleeding history for a patient with hemophilia as 1st presentation range from: (figure 1.3) Musculoskeletal bleeding is the most prevalent type of bleeding with (87.8%), Epistaxis (4.9%), CNS bleeding (2.4%), and GI bleeding (4.9%).

Of the (46) hemophilia patients three of them (6.5%) developed inhibitors with two of them having high titers during the follow-up period and immune tolerance induction (ITI) therapy was started, theses 2 patients did not tolerate the ITI due to severe anaphylaxis and allergic reactions so they were started on emisizumab treatment with good tolerance and dramatic improvement regarding the bleeding history.

Hemophilia patients with severe factor deficiency or moderate cases with severe phenotype were classified into either on-demand treatment (2%) or patients on prophylaxis (98%).

The prevalence rate of bleeding history as the first presentation for a patient with RBD ranges from: (figure 1.3) The most prevalent type of bleeding is asymptomatic 11 (39.4%), then Epistaxis 9 (32.1%), musculoskeletal 3 (10.7%), CNS bleeding 2 (7.1%), and GI bleeding 3 (10.7%).

Patients who are asymptomatic at presentation constitute about 11(13.8%) of patients. They are investigated either due to family history accounting for 2 (18.2%) of patients or incidentally found during the preoperative screening coagulation lab tests in 9 (81.8%) of patients.

Among those patients with RBD, prophylaxis was initiated in (50%) of factor XIII using the CRYO. (60%) of factor X with the use of PCC complex once weekly, (33.3%) of fibrinogen deficiency with the use of FFP q10 days, and factor VII patient (9%) with factor seven prophylaxis once or twice weekly.

The indication of prophylaxis for these patients is mainly related to previous history of major bleeding CNS bleeding in (40%), and GI bleeding in (60%) of patients on prophylaxis with RBD.

The surgical procedures for the patient are distributed into minor or major with orthopedic procedures among the most common procedure in hemophilia patients 29 (36%) and tonsillectomy among factor VII deficiency patients 10 (12.5%), the remaining were 18 (22.5%) dental procedures, 3 (3.75%) CNS procedures.

Discussion

Inherited factor deficiencies are an important area for research and development of new drugs for the treatment and replacement of the deficient factor to prevent and treat bleeding episodes, recombinant factor VII, FVIII, FX, FXIII, and FIX concentrates, specific monoclonal antibodies and gene therapy are available now for those patients. [9]

The precise assessment of hemorrhagic manifestations is a main component in the diagnosis of bleeding disorders. Although the evaluation of hemorrhagic symptoms is a big challenge for both patients and treating physicians, this is due to the interpretation and documentation of hemorrhagic symptoms being subjective and varies. Some bleeding symptoms may be passed as normal or minimal either between family members or by some physicians.

The 2019 publication of the World Federation of Hemophilia (WFH) Annual Global Survey (AGS), is now a key tool to evaluate the burden of bleeding disorders worldwide.

It also documented the progressive improvement in diagnosis and use of factor replacement therapy globally.

Noting that Bleeding disorders are rare conditions, with around 195,263 patients with hemophilia, 80,302 with von Willebrand disease, and 49,083 with other bleeding disorders identified worldwide in 2019.

According to the AGS 2019, in Jordan around 447 patients with hemophilia were reported, 259 patients with VWD and 255 patients with other bleeding disorders including 1 patient with FI, 4 patients with FII, 12 patients with FV, 51 patients with FVII, 21 patients with FX, 37 patients with FXI, and 17 patients with FXIII.

Noting that according to our data patients with VWD were lower numbers than patients with hemophilia A, which was considered to be related to the diagnostic difficulties of these patients in our country, including laboratory difficulties, fewer hematology labs in Jordan, and undiagnosed cases with vWD because of mild bleeding symptoms so most of the patients referred to us were usually moderate to severe types with frequent bleeding history, and this also mentioned in previous two studies runs in Jordan by kamal and awaidi which report higher incidence in hemophilia A in comparison to the VWD due to the similar problem mentioned above and to overcome these struggles we need a national collaboration between different centers in Jordan.[10–11]

Queen Rania Hospital for Children is a tertiary hospital with an experienced team and specialized hematology lab for the diagnosis and management of inherited bleeding disorders, our ENT, dental, and pediatric surgery clinics have led to the early diagnosis of many rare bleeding disorders cases.9 (81.8%) of our asymptomatic rare bleeding disorders cases were diagnosed before surgical procedures, while 2(18.2%) were diagnosed by family history. The prophylactic treatment was first started for patients with severe hemophilia in Sweden in the 1960s and then become the standard of treatment worldwide.(12)

The current talks and studies for patients with hemophilia A and B discuss the prophylactic treatment in those patients and its efficacy in the prevention of bleeding episodes.(13) At our center, we also start our patients either on-demand management or prophylaxis according to the severity of factor deficiency and the availability of factor replacement therapy. According to the WFH 2019 annual report, the estimated percentage of patients on prophylaxis was 10% among those under 18 years old and also 10% among those over 18 years old in Jordan which is a very low percentage in comparison to other developed countries like Germany and France with 100% and 80% respectively of patients below 18 use prophylaxis treatment and in comparison to the regional countries like Egypt, Iraq and Saudi Arabia its around 5%,100%, and 30% respectively but all of these percentages are estimated and don't reflect the true percentages in this countries.(14)

And if we reflect the percentages according to our study we have (98%) of patients with severe or moderate hemophilia A and B but with severe bleeding behavior on prophylaxis and (2%) of patients still on-demand treatment which is higher than what was documented in WFH.

Consumption of factor concentrates is defined as the number of international units (IU) consumed per inhabitant in a certain country over 1 year and is expressed in IU per capita. The IU/inhabitant rate reflects the resources made available by a country's healthcare system to provide hemophilic patients with adequate treatment. The minimum factor VIII consumption level required to introduce prophylactic treatment in a country is estimated at 1 IU/inhabitant, which means around 20000 IU/patient. (15) In the 2019 WFH annual reports, per capita FVIII consumption in Jordan was 1.058.

Our country has been categorized in the lower middle-income economy category, according to these recommendations and WFH reports, we believe that our country has made great progress and improvement in the management of hemophilia patients.

Although the increased prevalence of rare bleeding disorders (RBDs) worldwide, knowledge about these bleeding disorders and their management is suboptimal; healthcare providers usually have a little diagnostic and treatment experience with some access to diagnostic labs required for accurate diagnosis. Therefore, patients usually experience increased morbidity and mortality due to delayed diagnosis limited access to the lab, and limited treatment options.

A hematology specialist is required for hemophilia treatment and follow-up which is generally adequate in our hospital.

In most cases, RBD managed by the (on-demand) approach means that replacement therapy is given immediately after bleeding onset. In clinically severe cases with bleeding or a specific deficiency state, and the associated long-term disability even when the patient is on-demand treatment, prophylactic treatment is considered in these cases.

Peyvandi et al[16]talks about the minimal factor levels required to remain asymptomatic for patients with RBDs, showing a large variation between different levels of coagulation factor deficiencies. Noting that patients who are heterozygous usually not considered to have a bleeding disorder, factor activity levels that are required to be symptomatic vary from 12 IU/dL for FV deficiency up to 56 IU/dL for FX deficiency. These threshold levels are now often used in clinical practice; however, they have not been validated in a separate patient population.

The treatment dose and the frequency depend on the recommended minimal hemostatic level of each deficient factor, its plasma half-life, and the severity of bleeding either treated or to be prevented. [17] 43 patients in our hemophilia group (93.5%) and 6 patients in our RBDs group (21%) have received prophylactic treatments. The use of prophylaxis in patients with RBDs is individualized according to the severity of the bleeding, the seriousness of the bleeding, and the frequent need for replacement therapy decided by the hematology team. In our study, (9%) of patients with FVII deficiency were given prophylaxis of rFVIIa weekly or twice a week, (50%) of patients with FX deficit were given PCC once or twice a week, (33.3%) of patients with fibrinogen deficiency were given cryoprecipitate every week, the indication of prophylaxis for our patients is related to previous serious bleeding mainly GI bleeding in 60% of patients and CNS bleeding in 40% of patients. Table 2

The development of inhibitors is the most challenging complication during treatment with coagulation factors replacement in patients with haemophilia A, the rate of inhibitor development in patients with hemophilia was (6.5%) and all were patients with hemophilia A no reported case in patients with hemophilia B. which is lower when compared to the reported rates of 20% to 30% in patients with severe hemophilia[18–19]. The explanations for this low rate of inhibitor development were lack of access to clotting factor concentrates and laboratory inadequacies. Additionally, we think that patients with transient inhibitors and low-responding inhibitors are missed due to the frequency of inhibitor testing.

The immune tolerance induction (ITI) therapy is a way to inhibitor eradication whereby the body's immune system begins to tolerate a therapy after daily doses of factor replacement are administered over time. Individuals who undergo ITI will receive daily doses of factor over a period of weeks, months, or in some cases, years. [20]

It was administered to 2 patients (twins) of our 3 patients with inhibitors. But unfortunately stopped due to severe reactions and anaphylaxis happen to both patients during the 1st two months.

One of them also developed bacterial endocarditis (central venous catheter-related during the ITI period so he needs a long hospitalization time.

And after that, the patients were sent home with a plan to give on-demand rFVII as bypassing agent during bleeding episodes but this approach didn't prevent recurrent joint bleeding so we decide to start them on Hemlibra contains the drug emicizumab, which monoclonal antibody FDA approved in 2017 to be used in patients with hemophilia A with inhibitors than in 2018 approved for the patient without inhibitors also so this drug make a revolution in the management and prevention of bleeding episodes in these patients.[21]

Regarding our two patients, they are doing well on hemlibra with no bleeding episodes and no joint bleeding till 2 years after treatment one of the twins started to have severe GI bleeding need admission three times to the pediatric ICU during hospitalization he need a blood transfusion and bypassing agent with factor rVII and now we are working to investigate him more regarding the bleeding cause like meckles scan, RBC labeled scintigraphy because there are no other bleeding sites like joint or soft tissue bleeding so more investigation to look for a local cause rather than from his primary disease alone.

For RBDs patients, as the number of patients in need of prophylaxis was relatively low due to some factor deficiencies that lack specific concentrates here in Jordan like FX, FXIII, and fibrinogen so we follow the

on-demand treatment mostly unless the patient condition obligates the prophylaxis use.

Regarding the presentation of patients with RBD The prevalence rate of bleeding history as the first presentation for a patient with RBD ranges from: (figure 1.3)

The most prevalent type of bleeding is asymptomatic 11 (39.4%), then Epistaxis 9 (32.1%), musculoskeletal 3 (10.7%), CNS bleeding 2 (7.1%), and GI bleeding 3 (10.7%).

Patients who are asymptomatic at presentation constitute about 11(13.8%) of patients. They are investigated either due to family history accounting for 2 (18.2%) of patients or incidentally found during the preoperative screening coagulation lab tests in 9 (81.8%) of patients.

Noting that (60%) of patients with factor X deficiency present with GI bleeding in contrary to cases of factor VII deficiency (72%) of cases are diagnosed in the preoperative bleeding assay with no previous history of bleeding.

Clinical presentation among RBD patients vary significantly between disorders, and patients, even when affected with the same disorder and this is noted in different shared studies and documentations for these patients. [22]

You can see the summarized table below for our treatment approach in RBD:

Deficient factor	**Half-life**	**Replacement type (prophylaxis)**	**dose**	**Frequency (in prophylaxis)**	**On-demand treatment**
Fibrinogen	2-4 days	cryoprecipitate	1 unit/5 kg	Q7-10days	Cryo (1 unit/5kg)
Factor V	36 hours	FFP	15-20ml/kg	2 times/week	FFP (15-20ml /kg +platelet transfusion)
Factor VII	4-6 hours	rFVII	20-40mcg/kg	2 times/week	rFVII (15-30mcg/kg q4-6hrs)
Factor X	40-60 hours	PCC	20-40units/kg	2-3times/week	PCC (20-30units /kg)
Factor XIII	9-12 days	cryoprecipitate	1unit/5kg	Q3 weeks	CRYO 1unit/5kg

In the last 5 years, a dramatic increase in the administration of prophylactic treatment over these years shows that our clinic has been able to implement up-to-date treatment approaches.

Our challenge now is the genetic studies for these patients and the distribution in the regions should not be missed also Laboratory shortages including measurement of coagulation an essential issue that needs to be supported especially financially wise to cover all the required tests. Particularly for patients with vWD deficiency, who need more diagnostic procedures to be on an updated approach for the diagnosis and treatment of patients with inherited bleeding disorders is very important for those patients so they can live a normal life.

More and more collaboration is needed to help patients with RBDs achieve care like what's done for hemophilia patients, and finally, good support is needed for the introduction of genetic studies to our labs.

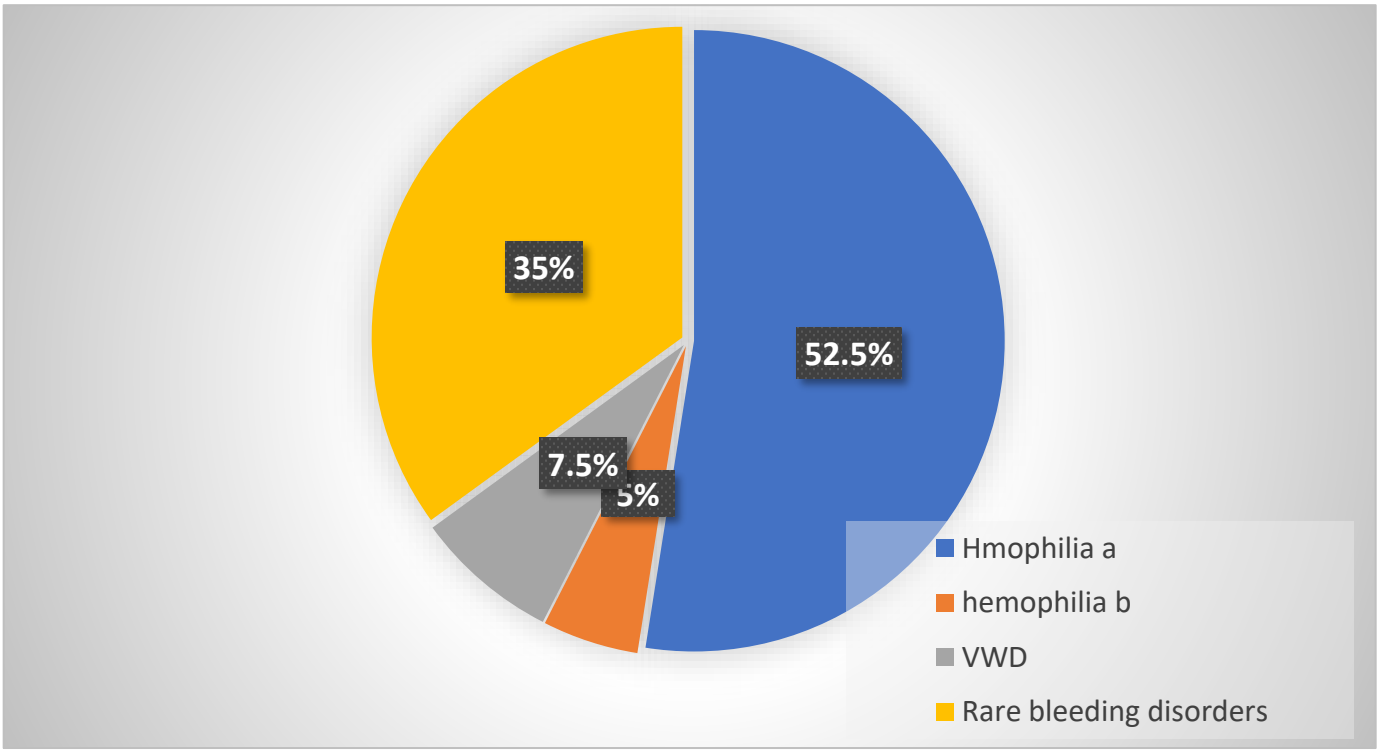

Figure 1.1: (number of patients with bleeding:)

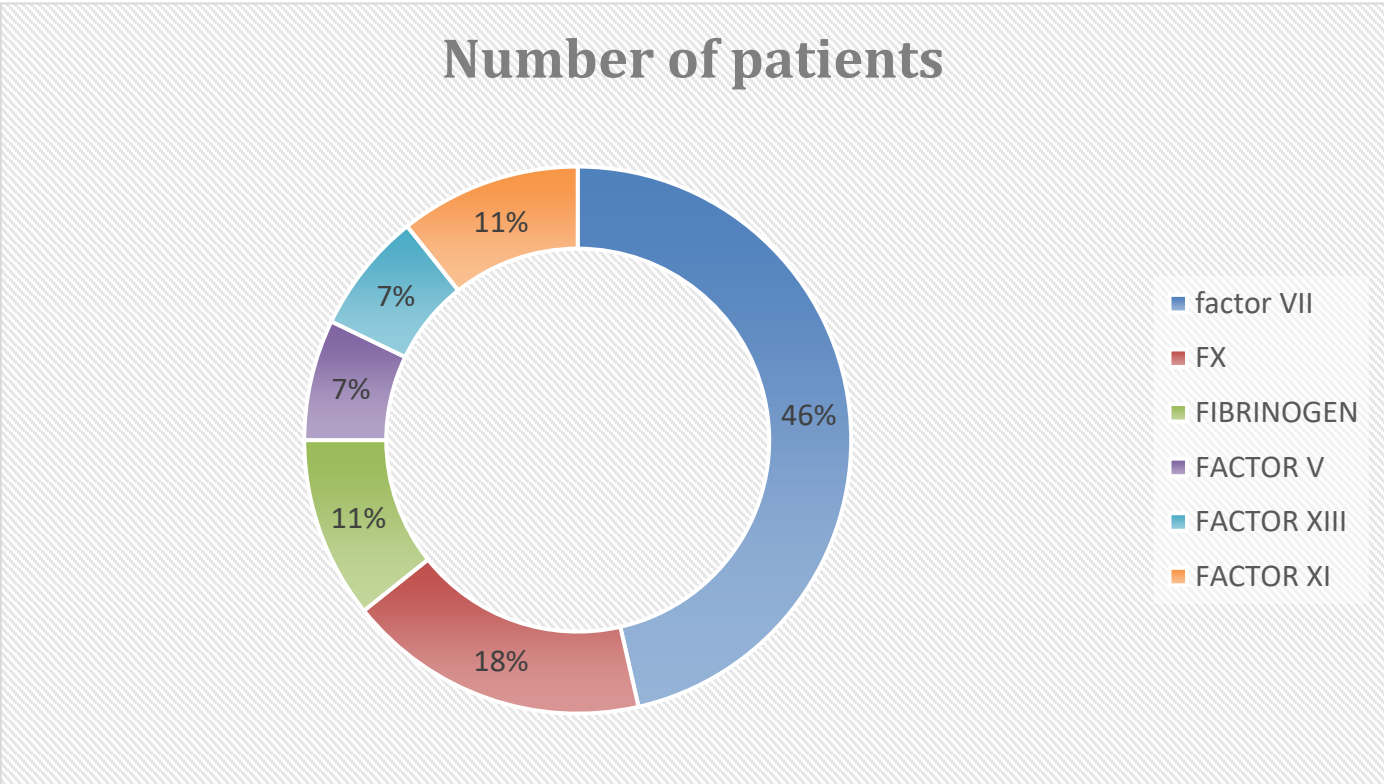

Figure 1.2: (number of patients with rare bleeding disorders)

Median age at diagnosis, years years (range 3months -14 years)		3.5
Sex, n (%):	Female (23.6%)	
	Male (76.4%)	
Factor activity, n (%):		
	Hemophilia A	hemophilia B
	<1% of normal activity (69%)	29 1(25%)
	1% to 5% of normal activity (26.2%)	11 3(75%)

	>5% of normal activity (4.8%)	2 0
Clinical presentations of hemophilias and vWD (N = 6)	Symptomatic	6
	Asymptomatic	0
Clinical presentations of rare factor deficiencies (n=28)	Symptomatic	17
	Asymptomatic	11
Inhibitor development in hemophilia A: 3 (6.5 %) hemophilia B		no patients in

Table 1. General Characteristics of Patients with bleeding:

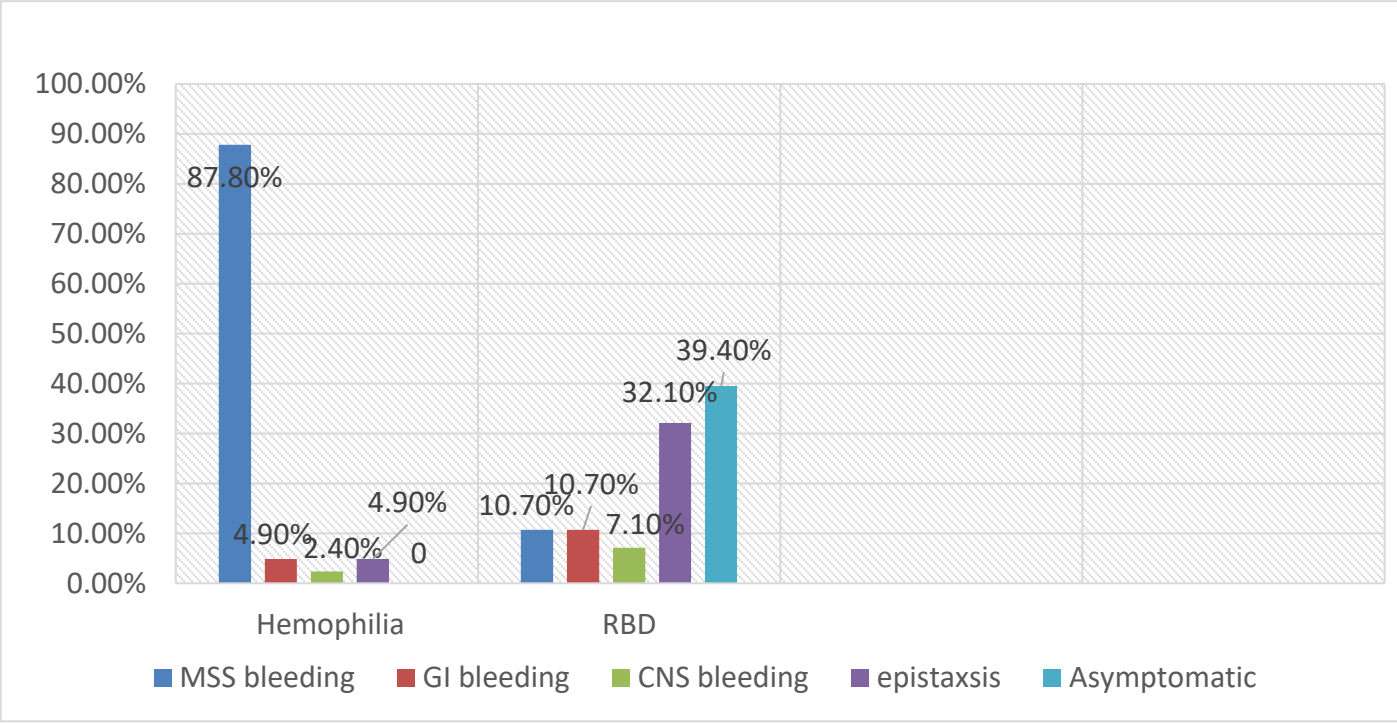

Figure 1.3: (the prevalence rate of bleeding history for patients with hemophilia & RBD) :

Factors	Number of patients	Common Presentation (n=number of patients)	Number of patients on prophylaxsis
Factor VII	13	Asymptomatic (11)	1
FX	5	GI bleeding (3)	3
Fibrinogen	3	Epistaxsis (2)	1
FV	2	Asymptomatic (2)	0
FXIII	2	CNS (1)	1
FXI	3	Epistaxsis (2)	0
FII	0	No reported cases	0

Table 2. General Characteristics of Patients with RBDs

Conclusion

The variety in the clinical presentation of IFD leads to significant diagnostic and therapeutic challenges, sharing our experience in treating patients with inherited factor deficiency will help.

To improve diagnosis and management of these bleeding disorders, especially in countries with limited resources and facilities.

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