Inherited Bleeding Disorders: A 14-year Retrospective Study

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Congenital bleeding disorders comprise a heterogeneous group of diseases that reflect abnormalities of blood vessels, coagulation proteins, and platelets. A 14-year retrospective study (1991-2005) was conducted for patients referred to the coagulation section of the Hematology Department (King Hussein Medical Center, Amman, Jordan), who had suffered from bleeding tendencies to assess the prevalence of bleeding disorders among Jordanians and to describe their clinical manifestations. Four hundred and three patients matched our criteria. All patients were screened with routine coagulation assays and a complete blood cell count; a factor assay was performed if indicated by the results of the screening assays. A total of 168 patients (41.6%) were diagnosed with a bleeding disorder caused by a factor deficiency, of which 17.1% were described as hemophilia A (n=69), 6.2% were described as vWD (n=25), and 4.2% were described as hemophilia B (n=17). A subset of the total patient population comprising 14.1% of the patients were diagnosed with a Rare Inherited Coagulation Deficiency (RICD), where 4.0% were FX deficient (n=16), 3.7% were FVII deficient (n=15), 3.7% were FV deficient (n=15), 2.5% were FXI deficient (n=10) , and 0.2% were diagnosed with afibrinogenemia (n=1).

Hemophilia A was the most prevalent disorder discovered among all bleeding disorders. Epistaxis was found to be the most frequent symptom among RICD patients. More hemostasis studies and surveys need to be undertaken in developing countries to estimate the relative numbers of all hemostasis abnormalities including factor deficiencies.

ABBREVIATIONS: aPTT = activated partial thromboplastin time; BT = bleeding time; CBC = complete blood count; KHMC = King Hussein Medical Center; PT = prothrombin time; RIPA = ristocetin induced platelet aggregation' RICD = recessively inherited coagulation disorders; vWF = Von Willebrand Factor; vWF:Ag = von Willebrand factor antigen; vWF:Rcof = vWF ristocetin cofactor.

INDEX TERMS: coagulation factors; haemophilia; inherited bleeding disorder; RICD; VWD.

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The spontaneous arrest of bleeding from a severed blood vessel is due to the formation of a clot produced by the constituents of blood at the site of injury. This hemostatic plug is formed within few minutes of trauma and results from a complicated process involving vascular responses, platelet aggregation, and activation of the blood coagulation mechanism.[1]

Inherited deficiencies or defects of the plasma proteins that are involved in blood coagulation can lead to life long bleeding disorders, the severity of which is inversely proportional to the degree of factor deficiency. The most frequent deficiencies are hemophilia A and B, due to inherited deficiency or defects of factors VIII and IX, respectively. Hemophilia A and B are both inherited as X- linked recessive traits, and have a prevalence in the general population of approximately 1 in 10,000 and 1 in 50,000, respectively, with no significant racial difference.[2] Hemophilia A and B comprise 95% to 97% of all the inherited deficiencies of specific coagulation factors. Hemophilia A and B are clinically indistinguishable from each other and occur in mild, moderate, and severe forms.

Von Willebrand Factor (vWF) is a protein required for the normal adhesion of platelets to the site of injured endothelium and needed for the mobility of factor VIII in the circulation.[1]

VWD is the most common inherited hemorrhagic disorder. VWD is associated with a defect in primary hemostasis and is also associated with a secondary defect in coagulation factor VIII.[3] VWD was first described in a five-year-old Finnish girl by Eric von Willebrand in 1926. The prevalence of vWD in the general population has been estimated as between 8-10 cases per 1,000 in the population, but it is possible that this is an underestimate since very mild cases may never be detected.[4]

Deficiencies in other coagulation proteins including factors V, VII, X, and XI are considered rare inherited coagulation disorders (RICD) and are transmitted as autosomal recessive traits in both sexes, with a frequency shown as homozygous forms in the general population (Table 1).[4,5] All of these factor deficiencies are rare except in populations where consanguineous marriages are common, such as in the Middle East, India, and Iran.

In order to define the prevalence of bleeding disorders caused by a factor deficiency and their associated clinical manifestations, the coagulation data of all patients suffering from bleeding tendencies were analyzed. These patients were referred to the hematology department of the King Hussein Medical Center (KHMC), one of the largest hospitals in Jordan, for investigation.

Table 1. Prevalence of factor deficiency in their homozygous states[4]

Deficient factor	Prevalence
VWD	1 in 100
VIII	1 in 10,000
IX	1 in 50,000
Fibrinogen (Factor I)	1 in 1,000,000
Prothrombin (Factor II)	1 in 2,000,000
V	1 in 1,000,000
VII	1 in 500,000
X	1 in 1,000,000
XI	1 in1,000,000
In Ashkenazi Jews	1 in 100
XIII	1 in 2,000,000

PATIENTS AND METHODS

The laboratory records and the clinical history of patients referred to the coagulation section of the hematology department at KHMC from 1991-2005 were reviewed for data acquisition. A total of 403 patients (ages ranging from 6 months-50 years) matched the criteria of our study, including 141 females and 262 males. Patients presented with the symptoms of mucocutaneous bleeding, epistaxis, ecchymosis, haematuria, post surgery trauma, and menorrhagia for females.

For all coagulation assays, venous blood samples were collected in tubes containing 0.109M (3.2%) trisodium citrate in a ratio of nine parts blood to one part anticoagulant,[6] and then centrifuged without delay at 1200-1500 xG for 15 minutes. Tripotassium EDTA (K_3EDTA) tubes were used to collect samples for a complete blood count.

All patients were screened for prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen level, all performed on the STA Compact coagulometer (Diagnostica Stago-Paris/France). Bleeding time (BT) was performed using a Simplate II device (Organon Teknika/Belgium). A complete blood count (CBC) was performed using the Sysmex XE-2100 (Sysmex Corporation/Japan). Quantitative functional factor assays (one stage factor assay)[7,8] were performed with human deficient plasma for specific factors using a specific deficient plasma (Diagnostica Stago –Paris/France). Available members of the patient's family were also investigated. For patients needing vWF screening, a vWD profile was performed which included: aPTT, factor VIII quantitative functional assay, von Willebrand factor antigen (vWF:Ag) using latex immunoassay (Liatest -Diagnostica Stago–Paris/France), vWF ristocetin cofactor (vWF:Rcof)[9,10] activity using vWFactor assay (Bio-Data-PA/USA), and ristocetin induced platelet aggregation (RIPA) using platelet aggregometry (Bio-Data-PA/USA).

One subtype of vWD, type IIb (also described as pseudo vWD with ristocetin hyper-responsiveness), was detected with RIPA using ristocetin doses of 0.5mg/ml, 0.75mg/ml, and 1.5mg/ml. The lowest dose considered for hyper-responsiveness in this study was 0.75 mg/ml. Other subtypes were not detected due to the fact that the vWF multimeric assay was not available in our laboratory.

RESULTS

Normal ranges were defined using 65 normal subjects recruited from the hospital staff (35 male and 30 female). Patients evaluated for factors VIII, IX, vWF:Ag, and vWF:Rcof with a result

50% concentration of normal or less were considered to be deficient. Patients evaluated for factors II, V, VII, X, and XI with 60% concentration of normal or less were considered to be deficient.

Patients with a factor concentration of <1% were considered as severely deficient, 1-5% concentration were considered as moderately deficient, and a concentration of >5% but less than 50% were considered as mildly factor deficient for factors presented in this paper. The number of patients with a factor deficiency and associated severity are presented in Table 2.

A total of 168 patients (41.6%) were diagnosed with a bleeding disorder caused by a factor deficiency. The 168 patients with a factor deficiency are described below in specific factor deficient groups with associated frequencies. Factor VIII deficiency (hemophilia A) was found in 63 families (n=69), 17.1% the total. Von Willebrand Disease (vWD) was found in 11 families (n=25), 6.2% of the total; of these, 2 families were found with subtype IIb, the other 9 families were not sub typed due to the unavailability of the vWF multimeric assay. Factor IX deficiency (hemophilia B) was found in 15 families (n=17), 4.2% of the total. Factor X deficiency was found in 8 families (n=16), 4.0% of the total; one family of the factor X deficient patients was diagnosed after a female baby was delivered with severe CNS bleeding and was found to have <1% factor X activity. After investigating her parents (first cousins), both were found to have a mild factor X deficiency. One year later another child was born to this family and he was found to have 5% factor X activity; these parents had anther baby girl two years later and she was found to have 30% factor X activity. Factor VII deficiency was found in 13 families (n=15), 3.7% of the total; one family was diagnosed after their five-year-old child presented with haematuria and epistaxis, and after investigation, he and his brother and sister were found to have severe factor VII deficiencies. The parents (first cousins) of these children were found to have mild deficiency. Of the total of factor VII deficient patients, five patients had epistaxis, three had bleeding after dental extraction, two were diagnosed by chance during pre-operative coagulation screening assays, and all were found to have a mild factor VII deficiency. Factor V deficiency was found in six families (n=15), 3.7% of the total; of these, one family with six members was diagnosed by chance after pre-tonsillectomy hemostasis screening assays had been performed. The parents (first cousins) and one child have a mild factor V deficiency, and the three other children have severe factor V deficiency, although none of them complain of any symptom other than mild epistaxis in one member. Factor XI deficiency was found in nine families (n=10), 2.5% of the total. Afibrinogenemia was found in one patient (n=1), 0.2% of the total.

All hemophilia A and B patients were evaluated for inhibitors, and one patient with hemophilia A developed an inhibitor to factor VIII during the study. No patients diagnosed with hemophilia B had or developed a factor IX inhibitor.

Table 2. Total patients with inherited bleeding disorders according to diagnosis

Bleeding disorder	Number of families	Sex		Total	Severity			Age range (years)
		M	F		severe	moderate	mild	
Hemophilia A	63	69	-	69	46	17	6	½-24
Hemophilia B	15	17	-	17	6	8	3	2-17
vWD	11	12	13	25	-	-	-	5-50
Factor XI deficiency	9	4	6	10	4	3	3	15-40
Factor X deficiency	8	8	8	16	4	2	10	1/2-35
Factor VII deficiency	13	9	6	15	3	-	12	24-50
Factor V deficiency	6	7	8	15	2	3	10	5-30
Afibrino-genemia	1		1	1	1	-	-	1
Total	126	126	42	168	66	33	44	

DISCUSSION

A few studies have been carried out in Jordan to show the prevalence of bleeding disorders associated with factor deficiencies and their clinical manifestations.[11-13] This particular study was carried out to help best define the frequency of these bleeding disorders in this area of the world.

Hemophilia A and B clinically resemble each other, and both have a sex linked inheritance and identical manifestation. This retrospective study showed that hemophilia A was the most common inherited coagulation disorder found among our patients (17.1%), showing that hemophilia A is not a rare condition in Jordan. These findings are similar to the Awidi[11,12] findings. However, hemophilia B was found in 4.2% of the cohort, which is less common than hemophilia A. These figures are close to the figures found in adjacent countries such as Iran[14] and Iraq.[15] Most hemophilia A and B patients presented with bleeding after circumcision or with haemarthrosis.

Von Willebrand's disease (vWD) presents with a variety of clinical manifestations. The true prevalence of vWD has not been clearly established, which may be due to variability of clinical and laboratory manifestations. Some mild cases remain under diagnosed. There is limited information on vWD in the developing countries of this region. Many studies and surveys have been conducted to normalize the prevalence of reported numbers associated with severe hemophilia A in a defined population, where hemophilia A is less likely to be missed. These studies and surveys showed that in most countries, the ratio of patients with VWD to severe hemophilia A varied between 0.1:0.6 with a mean of 0.4, as opposed to an expected ratio of approximately 1.0 (as reported in the literature), suggesting the under diagnosis of VWD.[16] In this particular study, 6.2% of the patients were found to have vWD. In a study conducted in Jordan, Awidi [17] reported that the prevalence of vWD was 2.1/100,000 among the Jordanian population; this figure is smaller than the one found in this study. This discrepancy can be explained by a difference in the study criteria and the number of patients evaluated in both studies.

Clinical manifestations displayed by the vWD patients in this study included were ecchymosis, epistaxis, and menorrhagia. Additional studies are needed in all developed countries in this region to develop national registries to better estimate the real numbers of vWD patients.

Factor XI deficiency (sometimes referred to as hemophilia C) is a very rare disorder; however it is reported significantly in the Ashkenazi Jewish population.[18] The clinical manifestations of this deficiency are milder than those of either hemophilia A or B. It is interesting to find that nine families (n=10) in this study have this deficiency; this may be explained by the fact that Jordan is adjacent to Israel, which is a country with an Ashkenazi Jewish population. Three of the subjects have a severe factor XI deficiency, two of these patients presented with gum bleeding, and one of these subjects presented with menorrhagia. The other seven patients in this cohort were found to have a mild deficiency, and all presented with a different bleeding manifestation.

The natural history and spectrum of clinical manifestations of recessively inherited coagulation disorders (RICD) are not well described due to the fact that very few clinical centers have the opportunity to see a significant number of these rare patients.[4]

Hereditary deficiency of factor V is an uncommon disease that was first described in 1947 by Owner.[19] It is transmitted as an autosomal recessive trait. Investigating the clinical history of the family (n=6) with a FV deficiency diagnosed accidentally revealed that all children suffered from epistaxis and had episodes of ecchymosis. The other five families with FV deficiency presented with a variety of different bleeding symptoms; five presented with epistaxis, three presented with menorrhagia, and one presented with haematuria. Epistaxis was frequent in this cohort, even in patients with moderate and mild deficiency. In contrast, other symptoms of mucosal bleeding, such as haematuria, are relatively low in frequency. In this study, one patient presented with haematuria. These findings are similar to the common manifestation of FV deficiency found in the literature.[20]

Hereditary factor VII deficiency is the most common of the RICD.[4] This deficiency is transmitted by an autosomal incomplete recessive gene. The clinical picture of factor VII deficiency is extremely variable, and in this study there has been wide variety of the reported hemorrhagic manifestations of this deficiency. The most frequent symptoms reported in literature are epistaxis, menorrhagia, haematuria, and bleeding after dental extraction, as reported by Peyvandi and others.[21] The most prevalent symptom found in this study is epistaxis. This symptom is found more frequently with a platelet defect rather than that of a coagulation defect. The reason for this finding has not been explained yet. Some studies reported a prolongation of the bleeding time in patient with factor VII deficiency.[22]

Congenital deficiency of coagulation factor X was first described by Telferetal in 1956.[23] This deficiency has an autosomal recessive inheritance, usually diagnosed by a concomitant

prolongation of the PT and aPTT in patients who have had a bleeding diathesis. The disease is rare,[4] and has the most severe clinical manifestation.[24] The most frequent symptom of patients with factor X deficiency found in this study was epistaxis, and these findings are similar to other studies findings reported in the literature.[25] In this study, one patient was presented with severe CNS bleeding. This patient and all siblings were treated with fresh frozen plasma infusion therapy.

One patient was diagnosed with afibrinogenemia after he presented with umbilical cord bleeding. The investigators could not trace his family, therefore they were not screened.

As demonstrated, epistaxis is the most frequent symptom found in all RIBD. This finding remains to be explained as to why this symptom is more frequent in RIBD than in hemophilia A and B, where haemarthrosis is the most common symptom.

In this study, 12 patients were diagnosed with RIBD by preoperative screening coagulation assays. After investigating the clinical history of these patients, all were found to have a minor bleeding tendency, but they had never complained of symptoms.

These RICD deficiencies accounted for 14.1% of all inherited bleeding disorders diagnosed in this 14-year retrospective study. This percentage figure is close to the figure found by Awidi, where he studied the prevalence of RICD in Jordan.[13]

CONCLUSION

As shown in the results and discussion, Haemophilia A was the most prevalent disease among all inherited bleeding disorders studied. Epistaxis is the most frequent symptom displayed among RICD patients.

Jordan is a country where consanguineous marriages are common, and as a result, a relatively high prevalence of RICD was found among our patients. Studies of these inherited bleeding disorders, many of which are rare and several of which result in a mild bleeding diathesis only, have significantly increased our understanding of normal hemostasis. Studying these bleeding disorders and their prevalence will enhance clinical practice, and help best define the frequency and diversity of these factor deficiencies. These findings will have a positive influence on patient care, and will especially enhance a proper and correct diagnosis of an inherited bleeding disorder.

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