

## Evaluation of the Clinical Status of Patients with Inherited Bleeding Disorders in Diyala-Iraq

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### Abstract

**Background:** Inherited bleeding disorders are rare diseases that are both complicated and expensive to manage, they are classified into: coagulation factor disorders, vessel wall defect and platelet disorders.

**Objective:** To show the pattern of Inherited bleeding disorders in Diyala-Iraq regarding frequency, distribution and complications.

**Patients and methods:** A review of all patient's records with bleeding disorders in the hemophilia care center in Al-Battol Teaching Hospital in Baquba during the period from the 1<sup>st</sup> of September 2014 to the 28<sup>th</sup> of February 2015 were included. All patients with a history of bleeding tendency were tested to confirm the diagnosis. History and clinical findings were recorded. Laboratory analysis included prothrombin time, activated partial thromboplastin time, bleeding time, and fibrinogen assay. Patients with prolonged activated partial thromboplastin time were tested for factors VIII and IX. If factor VIII was low, von Willebrand factor: antigen and von Willebrand factor: ristocetin cofactor was performed. Platelet aggregation studies were done when there was isolated prolonged bleeding time. All patients were tested for viral infection such as hepatitis B,C and Human immunodeficiency virus infection, patients with hemophilia A and B were evaluated for inhibitors.

**Results:** A total of 72 registered patients were reviewed in the hemophilia care center in Al-Battol teaching hospital. Inherited bleeding disorders identified in these patients include hemophilia A 57(79%), hemophilia B 5(7%), von Willebrand disease 5(7%), factor VII deficiency 3(4%); and platelet function defects 2 (3%). There were 68 (94%) males and 4 (6%) females. Hemarthrosis was the most frequent complaint in hemophilia A and B 41patient (66%) with knee hemarthrosis in 29 (71%) of them. Viral hepatitis C was positive in ten patients(14%), while hepatitis B positive in one patient(1.4%).The number of patients with inhibitors to Factor VIII was 3(5.3%)from total number of patients with hemophilia A.

**Conclusion:** Hemophilia A, hemophilia B and vWD are the commonly encountered inherited bleeding disorders in our governorate followed by other recessively transmitted disorders.

Hemarthrosis involving knee joint was the most common complication. Inhibitor was detected in a small number of patients.

**Keywords:** hemophilia A, von Willebrand's disease, platelet disorders.

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## Introduction

Inherited bleeding disorders are rare diseases that are both complicated and expensive to manage [1].

Deficiencies of coagulation factors have been recognized for centuries. Patients with genetic deficiencies of plasma coagulation factors exhibit lifelong recurrent bleeding episodes into joints, muscles, and closed spaces, either spontaneously or following an injury. The most common inherited factor deficiencies are the hemophilias, X-linked diseases caused by deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B) [2]. The complications of hemophilia stem from chronic bleeding into joints and muscles, which leads to severe deformities, arthritis, muscle atrophy, and contractures [3].

In addition, patients with hemophilia who received pooled-factor concentrates before the era of viral inactivation have complications related to transfusion transmitted infections, including HIV and hepatitis B and C [3]. Another serious complication of factor VIII infusion is the development of anti-factor VIII antibodies, which arise in about 20% of severe haemophiliacs [4].

Sometimes moderate and mild coagulopathies may remain clinically silent until detected on routine laboratory screening assay [5].

Rare congenital bleeding disorders due to deficiencies of other factors, including Factor II (prothrombin), Factor V, Factor VII, Factor X, Factor XI, Factor XIII, and fibrinogen are usually inherited in an autosomal recessive manner [2]. These deficiencies are quite rare in most populations, with the prevalence of the presumably homozygous forms ranging from 1:500,000 for Factor VII deficiency to 1 in 2,000,000 for prothrombin and FXIII deficiencies [2]. In areas where

consanguineous marriages are frequent, such as the Middle-East and southern India, these coagulation disorders are more frequent and together reach prevalences higher than those of haemophilia B, representing a significant clinical problem [6].

Von Willebrand disease (vWD) is the most common inherited bleeding disorder. Estimates from laboratory data suggest a prevalence of ~1%, but data based on symptomatic individuals suggest it is closer to 0.1% of the population [2].

Diyala was one of the eastern governorate in Iraq, the total population about 1,500,000 (one and half million) [7], it consists of 5 districts (Baquba, Al-mukdadiah, Al-khalis, Khanaqin and Baladrus). Consanguineous marriages are frequent among the families here.

This study design to show the pattern of inherited bleeding disorders in Diyala-Iraq regarding frequency, distribution and complications.

## Patients and Methods

This study was done for the period from the 1<sup>st</sup> of September 2014 to the 28<sup>th</sup> of February 2015. The medical records of 72 patients with inherited bleeding disorders registered in the hemophilia care center at Al-Battol teaching hospital in Baquba city, aged from 3 to 72 years old, the median age 15.5 year, 68 were males (94%) and 4 were females (6%), were reviewed. History and clinical findings were recorded and Patients with a history of bleeding tendency were tested to confirm the diagnosis.

Laboratory analysis included prothrombin time (PT), activated partial thromboplastin time (APTT), bleeding time (BT), and fibrinogen assay. Patients with prolonged (APTT) were tested for factors VIII (FVIII) and IX (FIX) level. If FVIII level was low, von Willebrand factor: antigen (vWF:Ag) and von Willebrand

factor:ristocetin cofactor (vWF:RCo) were performed, and if (PT) prolonged FVII assay were done. Platelet aggregation studies were done when there is isolated prolonged (BT).

All patients were evaluated for hepatitis B, C and HIV infection using Enzyme linked immunosorbent assay (ELISA), (biokit type, Spain). While patients with hemophilia A and B were evaluated for inhibitors by mixing patient plasma with normal plasma if prolonged (APTT) not corrected so inhibitors were present.

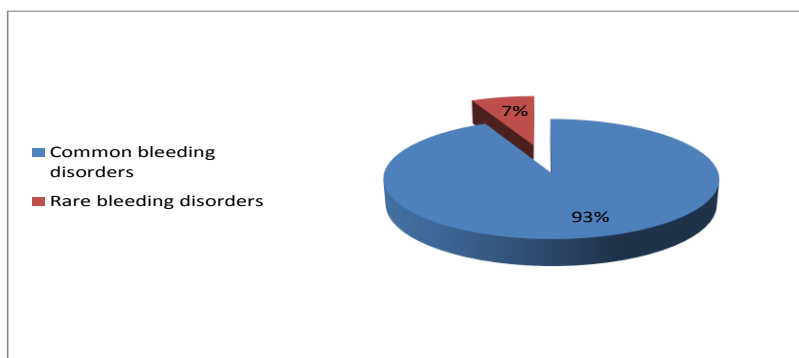
**Statistical analysis.** All statistical analysis was done by using statistical

package for social sciences (SPSS) version 20.

**Results**

The total number of cases with inherited bleeding disorders were (72), 68 were males (94%) and 4 were females (6%).

Those with common bleeding disorders (HA, HB, von Willebrand's disease [vWD]) form 67 (93%), while those with rare bleeding disorders [deficiency of coagulation factor VII and platelet disorder (Glanzmann thrombasthenia)] form 5 (7%),and as shown in figure(1).



**Figure (1):** The distribution of the patients into common and rare inherited bleeding disorders.

Hemophilia A was the most common bleeding disorder 57 patient(79%) followed by Hemophilia B 5patient (7%) and von

Willebrand disease 5 patient (7%) as shown in table (1).

**Table (1):** The distribution of inherited bleeding disorders according to the diagnosis.

Diagnosis	Number of patients	Percentage %
Hemophilia A	57	79%
Hemophilia B	5	7%
vonWillebrand disease	5	7%
Factor VII deficiency	3	4%
Glanzmann thrombasthenia	2	3%
<b>Total</b>	<b>72</b>	<b>100%</b>

So the prevalence of hemophilia A and hemophilia B was 7.6 and 0.67 respectively per 100,000 live male births in Diyala.

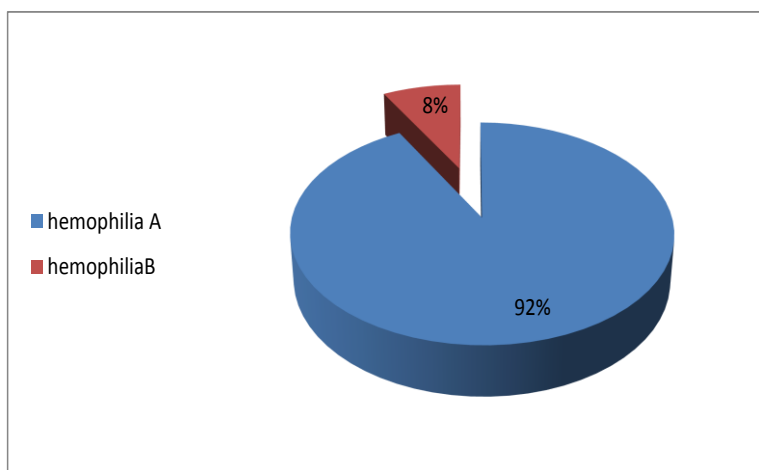
Most cases of inherited bleeding disorders were reported from Baquba and Khalis cities (35%) and (33%) respectively and as shown in table (2).

**Table (2):** The distribution of the patients with inherited bleeding disorders over the districts of Diyala governorate.

Inherited bleeding disorder	Baqubah NO. %	Al-Khalis NO. %	Al-Muqdadia NO. %	Khanaqin NO. %	Baladriz NO. %	Total NO. %
Hemophilia A	20 (28%)	22 (31%)	7(9%)	4 (6%)	4 (6%)	57(79%)
Hemophilia B	2 (3%)	1 (1%)	2 (3%)	0 (0%)	0 (0%)	5 (7%)
Vonwillebrand disease	3 (4%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	5 (7%)
Factor VII deficiency	0 (0%)	1 (1%)	2 (3%)	0 (0%)	0 (0%)	3 (4%)
Glanzmann thrombasthenia	0 (0%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)	2 (3%)
<b>Total</b>	25 (35%)	24 (33%)	13(18%)	5 (7%)	5 (7%)	N=72(100%)

The majority of hemophilia cases in our study were hemophilia A 57(92%) while the

remaining was hemophilia B 5(8%) and as shown in figure (2).



**Figure (2):** The distribution of patients with hemophilia.

The distribution of the patients according to the age show that 31patient (43%) were less than 15years old while 2 patients(2.8%)

were above 54 years old and as shown in table (3).

**Table (3):** The age distribution in patients with inherited bleeding disorders.

Diagnosis	< 5	5-14	15-24	25-34	35-44	45-54	>54	Total
Hemophilia A	6	18	20	9	0	2	2	57
Hemophilia B	1	2	1	1	0	0	0	5
Vonwillebrand disease	1	1	1	0	1	1	0	5
Factor VII deficiency	1	0	1	1	0	0	0	3
Glanzmann thrombasthenia	0	1	1	0	0	0	0	2
<b>Total</b>	9	22	24	11	1	3	2	72

Hemarthrosis was the most frequent complaint in hemophilia A and B 41 patient (66%), while knee joint was the most

common joint affected 29 patient (71%) of them.

Ten patients (14%) were hepatitis C positive, one patient (1.4%) was found to be hepatitis B positive and no patient with HIV positive test.

Mixing study revealed 3 patients with inhibitors to Factor VIII (5.3%) from total patients with hemophilia A, with no inhibitors to Factor IX were present.

## Discussion

The prevalence of hemophilia A and hemophilia B have been estimated as 10.5 and 2.8/100,000 male births, respectively. The prevalence of HA per 100,000 males in developed countries is  $12.8 \pm 6.0$  (mean $\pm$ SD) while it is  $6.6 \pm 4.8$  in developing countries [8, 9]. The prevalence of hemophilia in developing countries is less than that in both developed countries and the average international incidence [10]. Literature reviews imply that the incidence of HA and HB is the same in all racial and population groups and has been estimated to be 20 per 100,000 male births [8, 11].

The prevalence of HA has been reported for only three of ten countries in Asia and ranges from 2.9-3.6 per 100,000 males [11]. The possible reasons for under-diagnosed bleeding disorders in developing countries may be lack of diagnostic capabilities and insufficient public awareness of abnormal bleeding [12].

In this study a total number of patients with inherited bleeding disorders were 72. Most cases were reported in male (94%) and this is because that most of the patients had hemophilia which is X-linked disorder affect mainly male. This result in agreement with a study done by Islam and Quadri in Saudi Arabia 1999 [13] which show that 87% of the cases were male.

The common inherited bleeding disorders (hemophilia A, hemophilia B and Von willebrand disease) constitute 93% of the total number of patients and this result agree with another study done by Abdul-Karim and

Mohammed in Iraq 2010 [14]. Which show that common inherited bleeding disorders constitute (90.1%) and another study done by Galila and Soheir in Saudi Arabia 2012 [15]. Which show that common inherited bleeding disorders constitute (94.4%), but it's higher than studies done by Mansouritorghabeh and his colleague in Iran 2013 [16]. And another study done by Borhany and his colleague in Pakistan 2010 [17]. Which show that common inherited bleeding disorders constitute (77.5% and 64%) respectively.

Hemophilia A was the most common inherited bleeding disorder in this study 57(79%). and this was similar to other studies done by Galila and Soheir (2012) in Saudi Arabia, Mansouritorghabeh and his colleague in Iran during 2013, Borhany and his colleague in Pakistan 2010 and Gupta and his colleague in India 2005 [15, 16, 17, 18]. Which shows that hemophilia A was the most common inherited bleeding disorder in (48.4%,51.9%,37.2% and 42.4%) respectively.

The prevalence of hemophilia A appear in this study (7.6 per 100,000 live male birth) is higher than the prevalence reported from Iraq, Jordan, Pakistan and India at 2006 which show the prevalence (3.6, 6.9, 1.6 and 1.7 per 100,000 male) respectively, while it is lower than the prevalence in Egypt, Iran and Italy which show the prevalence at 2006 (8.7, 11.2 and 9.4 per 100,000 male) respectively [7].

The highest number of patients were from Baquba and Al-Khalis cities {25(35%) and 24(33%)} respectively, and this may be due to high density of people in these two cities or may be related with more consanguineous marriage there.

Von Willebrand disease was the second common inherited bleeding disorder in this study 5 patients (7%) with hemophilia B 5 patients (7%) and this finding agree with other studies done by Galila and Soheir in Saudi Arabia 2012[15], Mansouritorghabeh

and his colleague in Iran 2013 [16] and Borhany and his colleague in Pakistan 2010 [17], which show that Von willebrand disease the second inherited bleeding disorder but with higher frequencies (28.1%, 9% and 18%) respectively. This is may be due to the variable presentations of the disease, lack of awareness about the disease and inadequate facilities regarding diagnosis.

Inherited platelet function disorders in form of Glanzmann thrombasthenia was 3% in this study which is lowest than those in other studies done by Mansouritorghabeh and his colleague in Iran 2013[16], Borhany and his colleague in Pakistan 2010[17] and Gupta and his colleague in India 2005[18] which show inherited platelet function disorder in (6.9%,12.8% and39.4%) respectively.

Factor VII (FVII) deficiency form 4%from the total patients in our study and this finding agree with other study done by Abdul-Karim and Mohammed in Iraq 2010[14]which show factor VII deficiency in (3.7%)and studies done by Eid and his colleague in Jordan 2008[19] and Mansouritorghabeh and his colleague in Iran 2013 [16] which show factor VII deficiency in (3.7% and 3.4%) respectively, while it was lower than a study done by Dragani A et al in Italy 2008[20] which show factor VII deficiency in (27.9%).

The age distribution in this study show that 31patient(43%)were less than 15years old while 2patients(2.8%) were above 54 years old and this differ from a study done by Dragani and his colleague in Italy 2008[20] which show that (18.9%) were under 16years and (9.5%)were over 60 years old.

The most common complication in this study was hemoarthrosis which form (66%) and this is higher than result from other study done by Abdul-Karim and Mohammed in Iraq 2010[14] which show hemoarthrosis in (52.6%) and lower than results of studies done by Mansouritorghabeh and his colleague in Iran 2013 [16] and Borhany and

his colleague in Pakistan 2010[17] which show hemoarthrosis in (72.6% and 79.7%) respectively. Knee hemoarthrosis in this study appear in (71%).

Hepatitis C shown in this study in (14%) and it's higher than other studies done by Galila and Soheir in Saudi Arabia 2012[15] and Sajid and his colleague in Pakistan 2010[21]which show hepatitis C in (5% and 1.4%)respectively. And it's lower than a study done by Dragani and his colleague in Italy 2008[20] which shows hepatitis C in (21%).

Inhibitors to factor VIII appear in (5.3%) of cases and this agree with other study done by Dragani and his colleague in Italy 2008[20]which show inhibitors in (4%) and lower than a study done by Borhany and his colleague in Pakistan 2010 [17]which show inhibitors in (15%).

In conclusion, Hemophilia A, hemophilia B and vWD are the commonly encountered inherited bleeding disorders in our governorate followed by other recessively transmitted disorders.

Hemarthrosis involving knee joint was the most common complication. Inhibitor was detected in a small number of patients.

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