Study of Socio-demographic characteristics of patients with congenital coagulation disorders

Enas Talib Abdul-Karim[1] *PhD* , **Saad Fadhil Mohammed**[2] *MBchB*.

Abstract

Background: patients with genetic deficiencies of plasma coagulation factors exhibit life-long recurrent bleeding episodes into joints, muscles and closed space, either spontaneously or following an injury.

Objective: The present study aimed to determine the socio-demographic characteristics of patients with congenital coagulation disorders.

Methods: A cross-sectional study was conducted at the Centre of Congenital Coagulation Disorders in the Al-Mansour Pediatric Teaching Hospital in Baghdad for the period between 1st of March to 31st of August 2008.

The study sample was comprised of 243 patients with different congenital coagulation disorders who attended the Centre during the study period.

Data were collected through well structured questionnaire form introduced only by the researcher by interviewing with the patient or his/her relative or care giver.

Results: showed that hemophilia and Von Willebrand Disease (VWD) constituted the majority (90.1%), of the studied sample

The mean age of all patients was 14.31 ±10.42 years. About 77% of patients were from Baghdad governorate. Some families (15.6%) of the studied patients had three or more members with congenital coagulation disorders. For those patients aged ≥7 years, 41% of them had not attended or left school due to their disease. For those patients aged ≥18 years, 68.4% of them were unmarried, and 45.07% of them had no work due to their disease. Treatments were available to the majority (97.1%) of patients

Conclusions: The features in this study were similar to other studies in Mediterranean region and Western countries, except that the mean age of patients in this study was lower than that in other studies, blood groups showed no significant effect on types of congenital coagulation disorders, the disease showed adverse effects on all levels of education of patients

Key words: Study of Congenital coagulation disorders in Baghdad city

IRAQI J MED SCI, 2009; VOL.7 (3):94-106

Introduction

Coagulation disorders deal with disruption of the body's ability to control clotting.(1) Coagulation factor disorders can arise either from deficiency, usually congenital, of a single factor- e.g. factor VIII in hemophilia A or from multiple factor deficiencies which are often acquired, e.g. secondary to liver disease (2) Patients with genetic deficiency 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). Rare congenital bleeding disorders due to the deficiencies of other factors including factor II (prothrombin), factor V, factor VII, factor X, factor XIII, and fibrinogen are usually inherited in an autosomal recessive manner (3).

Hemophilia A (factor VIII deficiency) one out of every 5000 males worldwide; Christmas disease, or hemophilia B, is less common than hemophilia A. both are the most common severe inherited bleeding

[1]**Dept. Community Medicine, College of Medicine, Al-Nahrain University,** [2]**Medical city ,Baghdad, Iraq .**

Adress Correspondence to: Dr. Enas Talib Abdul-Karim.

E-Mail: enas_yhy@yahoo.com

Received:13th September 2009,Accepted:18th October 2009.

disorders [4], Von Willebrand's disease affects both males and females and is often diagnosed in children, the remaining defects, generally transmitted as autosomal recessive traits in both sexes, are rare, with prevalence of the presumably homozygous forms in the general population ranging from approximately 1 in 2 million to 1 in 500,000 [5]. Frequently these conditions produce life-threatening and limb- threatening complications. Moderate and mild coagulopathies may remain clinically silent until they are detected serendipitously on routine laboratory screening assay for global coagulation (e.g. PT or aPTT) or when these assays are ordered to evaluate the cause of abnormal bleeding or easy bruisability [6].

This study was done to assess the social and demographic characteristics of patients with congenital coagulation disorders.

Patients and methods

A cross-sectional study was conducted at the Centre of Congenital Coagulation Disorder (CCCD) in Baghdad city, this centre is the only centre in Iraq, was opened in 1997 and located within the Al-Mansour Pediatric Teaching Hospital which is connected with the General Administration of Medical City in Baghdad, it has a special Laboratory for diagnosis and wards inside the hospital for diagnosis and treatment for patients (from all age groups) who visited the centre from all over the country, The centre gives medical services to all patients with congenital coagulation disorder (CCD) who attend the centre except hemophilic patients with AIDS (referred to Al-Towaitha hospital for treatment), the centre also provides medical consultation about surgery for patients with CCD. The number of patients who attended the Centre each day was around 15 patients (new& old ones), and by the time the study was finished there were 1048 files for all patients who attended the Centre since it was opened until the end of the study period.

All patients (old and new cases) attending the CCCD for diagnosis, treatment, consultation, and follow up were included in the study during the period from the 1st of March to the 31st of August 2008, the work was for 5 days per week with a working hours of 4-5 hours/day. Two hundred forty three patients with different congenital coagulation disorders were included through well structured questionnaire form, data collected by the researcher only by direct interviewing with the patients or his\her parents or close relative. Information collected included different socioeconomic and demographic characteristics, family history, Some information were taken from the file of the patients like type of CCD, blood levels of factor VIII and factor IX for hemophilic patients, blood groups, , and availability of treatment.

In this study, the severity of hemophilia was classified on the basis of the patients baseline level of factor VIII or factor IX, patients having less than 1.0 unit/dl (<1%) of the specific clotting factor were considered as severe hemophilia, patients having 1-5 unit/dl as moderate hemophilia and patients having greater than 5 unit/dl were considered as mild hemophilia [4].

Data analysis was done using descriptive measures including mean, median, standard deviation, percentages, and test of significant done using chi-square. P value≤ 0.05 was considered significant.

Results

Hemophilia (A & B) and Von Willebrand disease constituted the majority (90.1%) of patients and corresponded to 64.6% of patients with hemophilia A, 16% hemophilia B, and

9.5% with Von Willebrand disease. Rare bleeding disorders (RBD) including factor 1, V, VII, X, and factor XIII deficiencies constituted 9.9% of the study sample. The proportion of cases with hemophilia A to B was 5:1 (table 1).

Generally, the studied sample included 90.1% males, and 9.9% females. All cases of hemophilia were males while the other congenital coagulation disorders include males and females totally in about equal number and even in each disease, the sex distribution is close in numbers, Of 243 patients; 239 (98.4%) were Arabic, while only 1.6% were Kurdish and they were hemophilic. All cases were Muslims, The mean age with standard deviation for all patients was 14.31± 10.42. The largest range of age was found among patients with factor VII deficiency 3.5 - 50 years. The least range of age 5 – 15 years was found among patients with factor XIII deficiency (Table 1).

Table-2: shows that 73.7% of patients with congenital coagulation disorders were below 20 years of age on attending the centre during the study period. It was found that most cases of hemophilia were either severe (66.3%) or moderate (22.5%), while the mild cases constituted only 11.2% of hemophilia patient. Statistically, the difference between the degree of severity of patients with hemophilia A and patients with hemophilia B was not significant P=0.494 (Table 3)

It was found that 187 patients (77%) were from Baghdad and 23% were from other governorates mainly those around Baghdad such as Dyala [26 patients,(10.6%)], Babil [6 patients,(2.5%)], Salahaddin [6 patients, (2.5%)], Anbar [5 patients, (2.1%)], and Wasit 2.1% (Table 4)

Out of 178 patients of ≥7 years of age; 7.3% were not attending primary school due to their diseases, and 41% had not attended or left school due to their diseases in comparison to 10.7% of patients who had not attended or left school not due to their diseases . Also it was noticed that slightly less than one third of them were either illiterates (9%) or just read and write (23%). On the other hand; 6 patients (3.4%) finished only the secondary school, and only 3 patients (1.7%) finished the university. Also 43.2% were still studying in different stages and more than half of them were still studying in primary school.(Table 5)

It was found that out of 79 patients above 18 years old; about two third (54 patients, 68.4%) of them were single, and about one third 31.6% of them were married.(Figure 1)

It was found that 45.07 had no work due to their diseases (Figure 2).

Generally speaking, slightly more than two third of patients (68.7%) had positive family pedigree and less than one third (31.3%) had negative family pedigree.(Table 6)

Figure 3 shows that:

- 134 patient's families (55.1%) had only one patient with CCD.
- 71 patient's families (29.2%) had two patients with CCD.
- About 10% of patients families had three patients with CCD.
- 6 patient's families (2.5%) had four patients with CCD.
- 8 patient's families (3.3%) had five patients with CCD.

It was found that 110 patients (45.3%) had blood group O, 70 patients (28.8%) had blood group B, 47 patients (19.3%) had blood group A, and 16 patients (6.6%) had blood group AB. Blood group showed no significant effect on type of CCDs, P value was 0.384.(Table 7)

During the study period, recombinant factor VII and factor IX were available to all patients with deficiencies of these factors.

Recombinant factor VIII was available to the majority of hemophilia A patients except 7 patients who received cryoprecipitate instead of recombinant F VIII concentrate When the latter was unavailable.(Table 8).

The median of times of attendance of all studied sample was 4 times per a year with a range of 0-39 times. Hemophilic patients had the largest range (up to 39 times) of attending the Centre per a year, while patients with factor X deficiency had the largest median of times (10 times) of attending the Centre per a year. The least median of times of attending the Centre was noticed in patients with Von Willebrand disease and patients with factor XIII deficiency which was only 2 times per a year.

Days of admission during the last 12 months: For all patients, the median was 5 days of admission per a year with a range of 0-55 days. The largest median of days of admission to the centre per a year was noticed among patients with factor X deficiency (13 days) , while patients with factor XIII deficiency or Von Willebrand disease had the lowest days of admissions to the centre (2 days, 3 days respectively) per a year, patients with hemophilia A were found to have the largest number of admission days (up to 55 days) per a year, and then followed by patients with hemophilia B (up to 38 days per a year). Other congenital coagulation disorders had admission of 20 days or less per a year. Treatment were available for 97.1% of patients with CCDs (Table 8)

Table 1: Distribution of patients with congenital coagulation disorders in the sample

Types of CCDs*	Sex				Race		Mean age ± SD**(year)	Range of age	total	
	Male		Female		Arabic	Kurdish				
	No	%	No	%					No	%
Hemophilia A	157	100	---	----	154	3	14.95±10.3	5 m***-43y****	157	64.6
Hemophilia B	39	!00	----	-----	38	1	10.313.29±	7 m-41 y	39	16.0
Von Willebrand disease	10	43.5	13	56.5	23	---------	11.29± 8.3	1 y-35 y	23	9.5
Factor I deficiency	4	66.7	2	33.3	6	-------	13.27 ±7.9	1.5 y-21 y	6	2.5
Factor V deficiency	0	-----	1	100	1	---------	18.25	18 y	1	0.4
FactorVII dificiency	4	44.4	5	55.6	9	------	15.8±16.3	3.5 y50 y	9	3.7
Factor X deficiency	2	66.7	1	33.3	3	-------	23.8 ±17.1	6 y-40 y	3	1.2
Factor XIII deficiency	3	60	2	40	5	-------	8.6 ±3.7	5 y-15 y	5	2.1
Total	219	90.1	24	9.9	239	4	14.3 ± 10.4	5 m-50 y	243	100

*CCDs= congenital coagulation disorders
**SD=Standard Deviation
*** m=months
**** y=years

Table 2: Distribution of congenital coagulation disorders by age

Age (years)	Hemophilia A		Hemophilia B		Von Willebrand disease		Rare inherited bleeding disorders		Total	
	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
< 1	2	0.82	2	0.82	-		-		4	1.64
1-4	29	11..93	10	4.12	5	2.06	5	2.06	49	20.17
5-9	28	11.53	7	2.88	7	2.88	7	2.88	49	20.17
10-14	32	13.17	6	2.47	5	2.06	2	0.82	45	18..52
15-19	22	9.05	3	1.23	3	1.23	4	1.65	32	13.16
20-29	28	11.52	8	3.3	2	0.82	3	1.23	41	16.87
30-49	16	6.58	3	1.24	1	0.41	3	1.24	23	9.47
Total	157		39		23		24		243	100

Table 3: Degree of severity of hemophilic patients in the studied sample

Degree of severity	Hemophilia A		Hemophilia B		Total		χ^2	P value
	Freq	%	Freq	%	Freq	%		
Mild	17	10.8	5	12.8	22	11.2	1.41 df=2	0.494
Moderate	38	24.2	6	15.4	44	22.5		
Severe	102	65.0	28	71.8	130	66.3		
Total	157	100	39	100	196	100		

Table 4: Governoratal distribution of patients with congenital coagulation disorders

Governorates	No. of patients	%
Baghdad	187	77
Dyala	26	10.7
Babil	6	2.5
Salahaddin	6	2.5
Anbar	5	2.1
Wasit	5	2.1
Najaf	2	0.8
Al-Quadessia	1	0.4
karbala	1	0.4
Mesan	1	0.4
Basrah	1	0.4
Al-Mothanna	1	0.4
Nainawa	1	0.4
Total	243	100.0

Table 5: Schooling situation and educational status of patients ≥7 years old with congenital coagulation disorders

Educational level	Still studying	Reason for not obtaining optimal educational level		Finishing secondary or university study
		Leave school due to disease	Leave school for other causes	
Not attending school (n=16)	-	13 (81.3%)	3 (18.7%)	-
Primary school (n=83)	42 (50.6%)	36 (43.4%)	5 (6%)	-
Intermediate school (n=49)	23 (46.9%)	17 (34.7%)	9 (18.4%)	-
Secondary school (n=20)	6 (30%)	6 (30%)	2 (10%)	6 (30%)
University (n=10)	6 (60%)	1 (10%)	-	3 (30%)
Total (n=178)	77 (43.2%)	73 (41%)	19 (10.7%)	9 (5%)

Table 6: Family pedigree of patients with congenital coagulation disorders

Congenital coagulation disorders	Family pedigree			
	yes		no	
	No.	%	No	%
Hemophilia A	116	73.9	41	26.1
Hemophilia B	27	69.2	12	30.8
Von Willebrand disease	12	52.2	11	47.8
Rare inherited bleeding disorders	12	50.0	12	50.0
Total	167	68.7	76	31.3

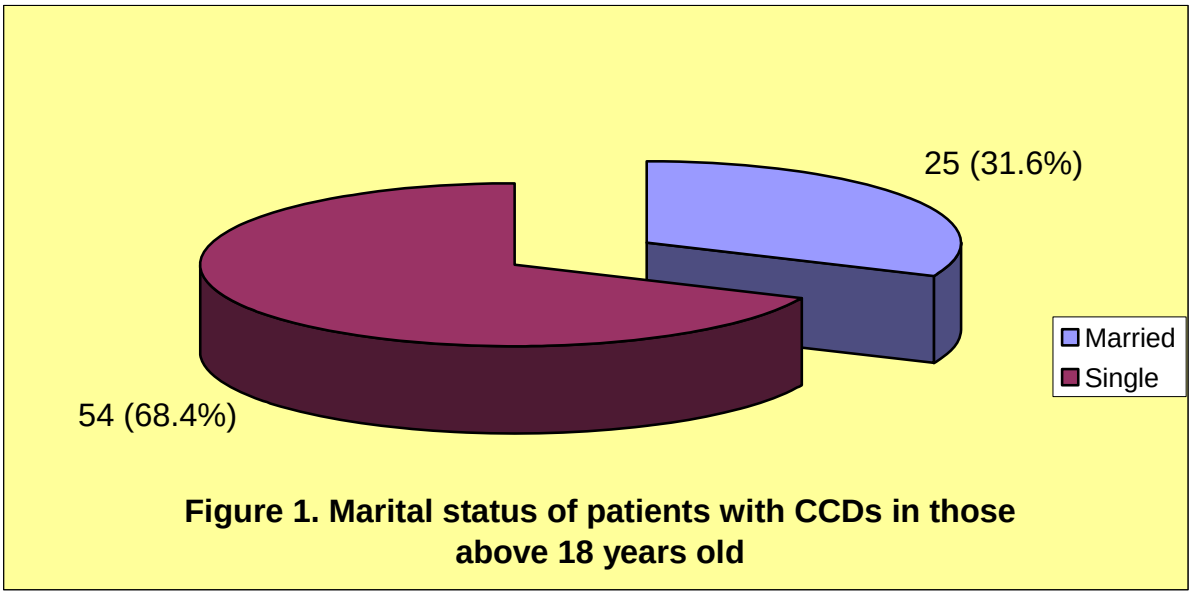

Figure 1. Marital status of patients with CCDs in those above 18 years old

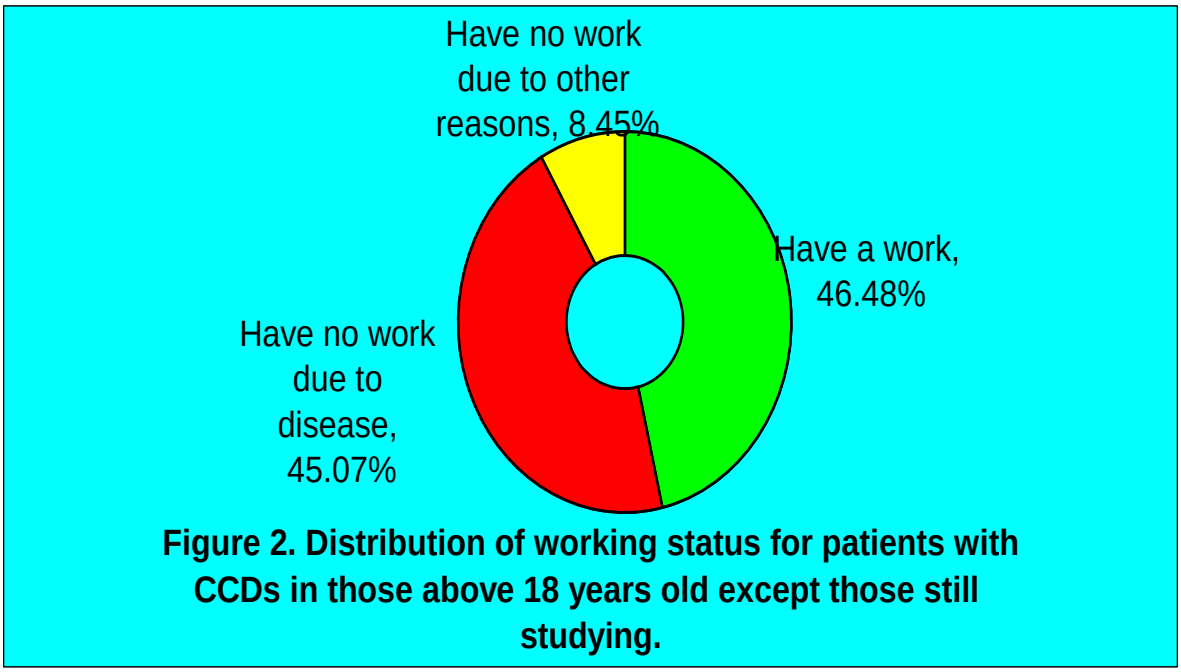

Figure 2. Distribution of working status for patients with CCDs in those above 18 years old except those still studying.

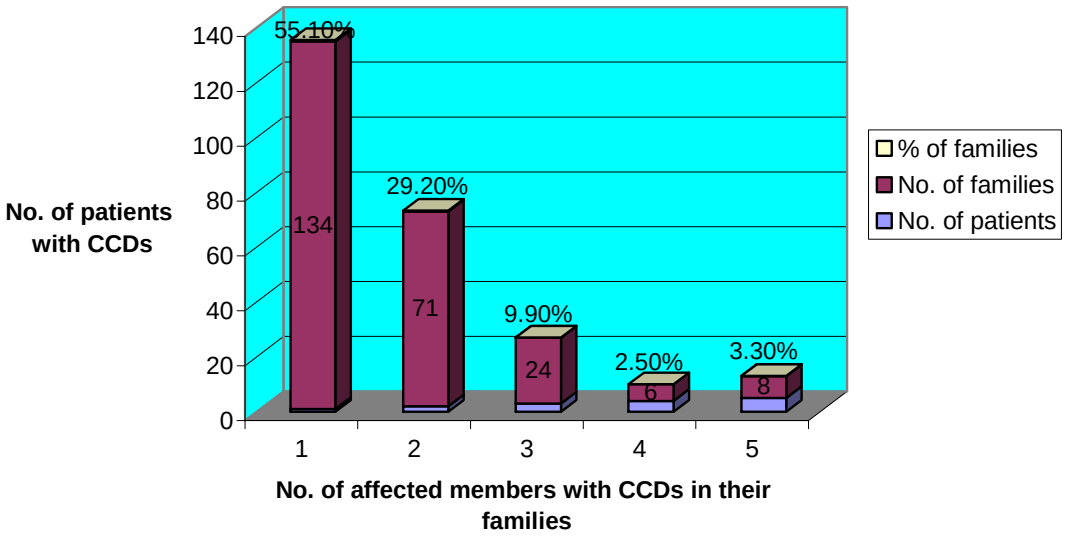

Figure 3. Ditribution of the number of affected members with CCDs within their families

Table 7: Blood group distribution among patients with congenital coagulation disorders

Blood group	Hemophilia A	Hemophilia B	Von Willebrand disease	Rare bleeding disorders	Total	χ^2	P value
A	32	8	6	1	47 (19.3%)	9.6 df=9	0.384
B	45	10	6	9	70 (28.8%)		
AB	10	1	1	4	16 (6.6%)		
O	70	20	10	10	110 (45.3%)		
Total	157	39	23	24	243		

Table 8. Distribution of times of attendance and days of admission to the Centre during the last 12 months for patients with CCDs

Types of CCDs*	Times of attendance to centre during last 12 months		Days of admission to centre during last 12 months		Treatment availability*			
	Median	Range	Median	Range	Yes	%	No	%
Hemophilia A	5	0-39	6	0-55	150	95.5 %	7	4.5
Hemophilia B	4	0-30	6	0-38	39	100	--	----
Von Willebrand bisease	2	0-9	3	0-17	23	100	----	----
Factor I deficiency	6	2-12	6	2-14	24	100	----	----
Factor V deficiency	1	------	1	-----				
Factor VII deficiency	5	1-20	6	2-14				
Factor X deficiency	10	2-20	13	2-20				
Factor XIII deficiency	2	1-6	2	1-7				
Average	4	0-39	5	0-55				
Total					236	97.1	7	2.9

* Treatment availability for haemophilic patients includes only recombinant factors

Discussion

This is the first study on the socio-demographic aspects of congenital coagulation disorders in the Centre of Congenital Coagulation Disorders in Iraq, which was established in Baghdad city on 1997, that make it difficult to compare the result of this study with other Iraqi studies except with the only two studies found; one related to the prevalence of viral hepatitis markers in patients with hereditary bleeding disorders carried on 1997 by Dilshad Saber [7], and the other was a prospective on-going study by AL-Mondhiry [8] and was published at Thrombosis and Hemostat Journal 1977. In this study, the majority of patients (90.1%) had either hemophilia or Von Willebrand disease and this result is similar to studies in Iraq [8], KSA[9], Iran [10], Poland [11], Pakistan [12], Brazil [13], Europe [14], and Thailand [15]. In this study, hemophilia-A was the most prevalent (corresponded to 64.6%) among patients with congenital coagulation disorders. This result was in agreement with studies in Iraq [8], Saudi Arabia [9], Iran [10], USA [16], Canada [17], Italia [18], Poland [11], Brazil [13], Thailand [15], and India [19]. The ratio of hemophilia-A to B was 4:1, this result was similar to other studies in which the ratio range 3.7:1 to 6.5:1 as such that in:

Iran by Mehdizadeh et al., [20] the ratio was 5: 1.

India by Kulkarni et al., [19] the ratio was 5.3: 1.

USA by Michael Soucie et al., [16] the ratio was 3.7: 1.

Brazil by Rezende et al., [13] the ratio was 5: 1.

Canada by Ronald O. Barr et al., [17] the ratio was 4: 1.

Spain by Aznar et al., [21] the ratio was 6.5: 1.

Poland by Windyqa et al., [11] the ratio was 6: 1.

Most cases of hemophilia were severe (66.3%), followed by moderate (22.5%), and mild (11.2%). This distribution of severity, as expected, reflect that the severe cases attended the Centre more frequently than moderate or mild cases and caused increase in their prevalence. This result was in concordance with report of National hemophilia foundation [22]. The result that severe form was more prevalent than the other form was in agreement with a study in USA [16], Italia [18], Poland [11], Canada [18], Brazil [13], and Netherlands [23]. In this study, the proportion of moderate and mild forms had disagreement with other studies [9, 20], this discrepancy in the prevalence of degree of severity of hemophilia in different studies may be related to differences in the types of studies and on the criteria on which hemophilia was defined.

In von Willebrand disease, male to female ratio was 1: 1.3 and this was in agreement to a study in Brazil [13] with a ratio of 1: 1.5. In this study, 47.9% of patients with VWD were between 10-49 years old in contrast to 76.7% in a study in Brazil conducted by Rezende et al. [13] This discrepancy may be due to that about half of patients (52.2%) in this study were between 1-10 years of age. `In rare inherited disorders, the most common one was factor VII deficiency and constituted 37.5% of rare bleeding disorders. This result was in agreement with a study in Iran conducted by Karimi et al. [10], a study in Pakistan [12] and a study in Poland [11].

While rare inherited bleeding disorders (RIBD) was found in this study to constitute the minority (9.9%) of the studied sample and is similar to studies in Iraq [8] (11.3%), Iran[10] (9.1%), KSA[9] (14.3%), India [19] (12.5%), and Pakistan [12] (5.9%) , but is

more than studies in Europe [14] (3-5%), Brazil [13] (2.4%) , and Thailand [15] (3.86%). This discrepancy is most likely due to high rate of consanguinity marriages and large number of births per family in Iraq. It was slightly higher than that in Brazil (2.4%) [13], Europe (3-5%) [14] and Thailand (3.9%) [15]. In all these countries in addition to a study in North America and Canada conducted by Acharya [24] factor VII was the more prevalent among RIBD and in agreement to the result of this study.

The mean age of all patients on examination in this study was 14.31±10.42 years which was less than a study in Iran carried by Mehdizadeh, et al.[20] (29.92±15.19 years), and another study also in Iran carried by Mohssen Nassirtoosi, et al.[25] with a mean of 26.6±12.1 years and most of the patients were in the third decade of life. It has been estimated that > 80% of patients older than 20 years of age are HCV antibody positive as of 2006 [3], in the present sample majority of patients are young ones who are born after 1986 which might indicate that some of them had already received non- virucidal factor concentrate, the study shows that 73.7% of patients were below 20 years old, while a study carried in Iran [20] showed that half of the population studied was younger than 24 years of age.

It was found that 77% of patients were from Baghdad, and 23% were from governorates other than Baghdad especially those governorates close to Baghdad geographically. This finding may be due to inaccessibility of patients from these governorates. The low levels of educational status of patients with CCDs may be explained by fearing of patients parents from getting trauma to their affected children in school and so prevent them from attending school, or due to frequent absences from school because of their frequent attendances and admissions to hospital.

Unfortunately, there were no other studies accessible for comparison.

It was found that 68.4% of all patients above 18 years old were unmarried. And apart from those who still studying, 53.5% had no work whether due to their disease or not. Also blood groups showed no significant effect on types of CCD. Unfortunately, there were no other studies accessible for comparison.

It was found that 29.2% of families had two patients, and 15.7% of families had more than two patients with this disorder. This finding is due to inherent nature of these diseases, large Iraqi family size, and sharply pointed to the need of proper education and genetic counseling for family planning for those families. Unfortunately, there were no other studies were accessed for comparison. In this study, family pedigree was negative in 26.1% and 30.8%of patients with hemophilia A and B respectively. This result was in agreement with what was published in USA [27] , and was in consistent with the hypothesis of Heldane [28] that lethal X-linked recessive disorders in approximately one third of patients and are due to spontaneous mutation, but this result was in disagreement with a study in Poland [11] which showed that about 50% of the hemophiliacs have no history of bleeding diathesis in the family.

When the study considered rare inherited disorders, the proportion of male (54.2%) and female (45.8%) in this study was in agreement to that found in a study in Pakistan [12] Family pedigree was positive in 50% of patients with RIBD. This finding was in agreement with a study in North America and Canada[24] and a study conducted by Herrmann et al on

subjects from Europe and Latin America with mutation in the factor VII gene[29] . Although about half of patients were with blood group O, there were no significant differences between the different types of CCDS regarding their blood group, this possibly could be due to sample size and also those with rare bleeding disorders were only 24 patients in the sample.

The median times of annual attendance to the Centre by patients with congenital coagulation disorders was 4 times, with a range of 0-39 times. Also these patients had a median of 5 days admission per a year with a range of 0-55 days of admission per a year. This reflect the high rate of attendance and admission of patients with congenital coagulation disorders to this Centre and it was mainly due to the nature of their diseases, treatment were available to 97.1% of patients with CCDs, which in some way reflect the support of the government to this centre in spite of the difficulties facing the country in the current situation.

There is a clear need for extensive study in the whole country to determine the exact prevalence and other epidemiological distribution of CCDS, a need to establish new centers in governorates other than Baghdad and planning for administering home-treatment (prophylaxis treatment) for patients with severe hemophilia.

References

1. Norris RN Teresa " Coagulation disorders" Gale Group Encyclopedia of Medicine. Dec. 2002, 29 May 2009. <www. lifesteps. com/gm/Atoz/ coagulation_ disorders. jsp>.

2. CRAIG J I O, McClelland D B L, LUDLAM C A. Blood disorders. In: Nicholas A Boon, Nicki R. Colledge, Brian R. Walker, editors. Davidson's Principles and Practice of Medicine. 20th ed. Philadelphia: Churchill Livingstone Elsevier; 2006. pp. 1055-6.

3. Bleeding and thrombosis. Harrison's Principles Of Internal Medicine, 17th ed., 18 Mar 2008, 30 May 2009. < www. harrisonpractice. com/practice/ub/view/Harrison_Principle_of_Internal_Medicine_17th-Edition/Coagulation_Disorders/395110/0 >.

4. Montgomery M. Robert and Scott J. Paul. Hereditary Clotting Factor Deficiencies. In: Richerd E Behrman, Robert M Kliegman, Hal B Jenson editors. Nelson Textbook Of Pediatrics.17th ed. USA: Saunders Elsevier; 2004. pp. 1657-1661.

5. Peyvandi F, Duga S, Akhavan S, Mannucci PM. Rare coagulation deficiencies. Hemophilia. 2002; 8: 308-321.

6. Kessler Craig M. Hemorrhagic Disorders. In: Lee Goldman, Dennis Ausiello, editors. Cecil Medicine 23rd ed. USA: Saunders Elsevier; 2008. Pp. 1301-14.

7. Saber M. Delshad: The prevalence of viral hepatitis markers in patients with hereditary bleeding disorders; submitted to Scientific Council of Medicine in partial fulfillment for the degree of fellowship of the Iraqi commission for medical specialization in internal medicine. Oct 1997

8. AL-Mondhiry HA: Inherited bleeding syndromes in Iraq. Thromb Haemost. 1977 Jun; 37(3):549-55

9. Islam S.I.A. and Quadri M.I.: Spectrum of hereditary coagulation deficiencies in Eastern Province, Saudi Arabia. Eastern Mediterranean Health Journal 1999; Vol. 5, issue 6: 1188-1192.

10. Karimi M, Yarmohammadi H, Asdeshiri R. Inherited coagulation disorders in Southern Iran. Haemophilia 2002 Nov; 8 (6): 740-4.

11. Windyqa J, Lopacink S, Stefanska E, Klukowska A. Hemophilia and other inherited blood coagulation disorders in Poland. Pol Arch Med Wewn 2004 Oct; 112 (4):1197-202.

12. Khalid S, Bilwani F, Adil SN, Khurshid M. Frequency and clinical spectrum of rare inherited coagulatopathies-a tricenter study. J Pak Med Assoc. 2008 Aug; 58 (8): 441-4.

13. Rezende SM, Pinheiro K, Caram C, Genovez G, barca D. Registry of inherited coagulopathies in Brazil: First report. Haemophilia 2009; 15. 142-149.

14. Gatt A and Chowdary P. Proceedings of the First Annual Congress of the European Associationfor Hemophilia and Allied Disorders. Haemophilia 2009; 15, 329-336.

15. Chuansumrit A, Mahasandana C, Chinthammitr Y. National survey of patients with hemophilia and other congenital bleeding disorders in Thailand. Southeast Asian J Trop Med Public Health 2004 Jun; 35 (2): 445-9.

16. Soucie J Michael, Evatt E Bruce, Jackson Debra, the hemophilia Surveillance System Project Investigators. Occurrence of

Hemophilia in the United States. Am J of Hematol 1998; 59 (4): 288-294.
17. Barr D Ronald, Saleh Mahassen, Furlong William, Horsman John, Sek Julia, Pai Mohan, Walker Irwin. Health status and health-related quality of life associated with hemophilia. Am J of Hematology 2002 nov; 71(3): 152-160.
18. Iorio A, Oliovecchio E, Morfini M, Mannucci PM, Association of Italian Hemophilia Centers Directors. Italian Registry of Hemophilia and Allied Disorders: Objectives methodology and data analysis. Haemophilia 2008 may; 14(3): 444-53.
19. Kurkarni M L, Nanda G. Hemophiliacs- a picture from a developing country: Karnataka, a south Indian state. Southeast Asian J Trop Med Public Health 1993; 24 Suppl 1 270-3.
20. Mehdizadeh M, Kardoost M, Zamani G, Baghaeepour M R, Sadeghian K and Pourhoseingholi M A. The Occurance of Hemophilia in Iran. Haemophilia 2009, 15, 348-351.
21. Aznar J A, Lucia F, Abad-Franch, Jimenez-Yuste V, Perez R, Batlle J, Balda I, Parra R, and Cortina V R. Hemophilia in Spain. Haemophilia 2009 May; 15(3): 665-675.
22. National Hemophilia Foundation (NHF). Hemophilia A (Factor VIII Deficiency). 2008. 30 May 2009. < http://www. Hemophilia. org/ NHF web/ Main Pgs./ Main NHF. >.
23. Denuijl I E M, Fischer K, Vander Bom J G, Grobbee D E, Rosendaal E R and Piug I. Clinical outcome of moderate hemophilia compared with severe and mild hemophilia. Haemophilia 2009 Jan; 15(1):83-90.
24. Acharya S S, Coughlin A, Dimichele D M, and the North American Rare Bleeding Disorder Study Group. Thrombosis and Haemostasis J 2004 Feb;2 (2): 248-256.
25. Nassirtoosi Mohssen, Lak Manije, Katayoun. Serum viral markers in Iranian patients with congenital bleeding disorders. Ann Saudi Med 2008; 28 (6) : 453-455.
26. Montgomery R. Robert, Gill Cox Joan, Scott J. Paul. Hemophilia and von Willebrand Disease. In: Nathan and Oski's editors. Hematology Of Infancy And Childhood. 6th ed. Philadelphia: Saunders; 2003. pp. 1547-1576.
27. Haldane J B S: The rate of spontaneous mutation of a human gene. J Genetic, London. 1935; 31:317.
28. Herrmann F H, Wulff K, Auerswld G, Schulman S, Astermark J, Batorova A, Kreuz W, Dollmann H, Ruiz-Saez A, Bosch N DE, and Salazar-Sanchez L. Factor VII deficiency: Clinical manifestation of 717 subjects from Europe and Latin America with mutations in the factor 7 gene. Haemophilia 2009, 15, 267-280.