Study of clinical characteristics, presentation, and complications among patients with congenital coagulation disorders

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ABSTRACT

الأهداف: دراسة العلامات السريرية، والمضاعفات التي تصيب المرضى المصابين بأمراض نزف الدم الوراثية المراجعين لمركز الأمراض النزفية الوراثية – بغداد – العراق.

الطريقة: أجريت دراسة مقطعية في مركز الأمراض النزفية الوراثية – مستشفى المنصور التعليمي للأطفال – بغداد – العراق وذلك خلال الفترة من مارس 2008 حتى أغسطس 2008م. تألفت عينة الدراسة من 243 مريض مصاب بمختلف الأمراض النزفية الوراثية. جمعت البيانات من خلال استبيان منظم، بالإضافة إلى الفحص الجسدي للمرضى بإشراف الطبيب المسؤول في المركز.

النتائج: يشكل المرضى المصابين بالهيموفيليا ومرض ڤون ويلليبراند (VWD) نسبة عظمى تقدر 90.1% من العينة. بينما يشكل المرضى المصابون بالإمراض الوراثية النادرة نسبة 9.9%. ظهرت الأعراض المرضية عند معظم المرضى (82.7%) وذلك خلال السنة الأولى من العمر. وكان 52.7% من مرضى العينة يعانون سريرياً من نزف في المفاصل خاصة المرضى المصابين بمرض الهيموفيليا و المرضى المصابين بمرض نقص العامل العاشر، وهذا التوزيع مطابق لتوزيع تقيد الحركة في المفاصل لعينة المرضى.

خاتمة: أن غالبية المرضى مصابين بالهيموفيليا، الغالبية العظمى لظهور الأعراض كان في الأعمار التي تتراوح بين 12–6 شهر وكان التشخيص الأعلى للمرض خلال شهر من ظهور الأعراض. كما أن غالبية المرضى المصابين بتقيد المفاصل يعانون من الهيموفيليا وحوالي 50% من المرضى كانوا يعانون من تقيد في ثلاثة مفاصل أو أكثر.

Objectives: To study the clinical characteristic, presentation, complications in patients with congenital coagulation disorders who attended the Congenital Coagulation Disorders Center, Baghdad, Iraq.

Methods: This cross-sectional study was conducted in the Center of Congenital Coagulation Disorders, Al-Mansour Pediatric Teaching Hospital, Baghdad, Iraq between March 2008 and August 2008. The sample comprised 243 patients with different congenital coagulation disorders. We collected the data through structured questionnaire form and carried out the physical examination of the patient under the supervision of the physician-in-charge at the center.

Results: Hemophilia and Von Willebrand Disease (VWD) constituted 90.1% of the sample, while rare bleeding disorders constituted 9.9%. Most patients (82.7%) have had onset of symptoms during the first year of life. Clinically, 52.7% of patients presented with hemarthroses were hemophiliacs and factors X deficiency. This distribution was also true for joint limitations.

Conclusions: Most patients were hemophiliacs and the highest prevalent of symptom was 6-12 months old, and the diagnosis of the disease was highest within one month after the onset of symptoms. Most patients with joint limitation was hemophiliacs and approximately 50% had limitation of 3 or more joints.

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Severe coagulation deficiencies, or coagulopathies, typically are characterized by the development of excessive bleeding, which could occur following minor injury or surgical trauma, these conditions could produce life-threatening and limb-threatening complication. Sometimes moderate and mild coagulopathies may remain clinically silent until detected on routine laboratory screening assay.[1] However, the occurrence of bleeding into the gastrointestinal and urinary tracts and particularly into weight-bearing joints is common[2] and especially intracranial hemorrhage, which accounts for most of mortality in all age groups.[3] This study was conducted to study the clinical presentation, and complication in patients with congenital coagulation disorders who attended the Coagulation Center in Baghdad city, Iraq.

Methods. This cross-sectional study was conducted at the Center of Congenital Coagulation Disorder (CCCD) in Baghdad city, this center is the only center 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, Iraq. 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 center from all over the country, the center gives medical services to all patients with congenital coagulation disorder (CCD) who attends the center except hemophilic patients with acquired immune deficiency syndrome AIDS (referred to Al-Towaitha hospital for treatment), the center also provides medical consultation on surgery for patients with CCD. Approval was obtained from the Center for Research and Educational Methods, Ministry of Health, and General Administration of the Medical city and Al-Mansour Pediatric Teaching Hospital. Fifteen patients attended the center each day (new and old), and at the end of the study we have a total of 1048 files. We included all patients (old and new cases) attending the CCD for diagnosis, treatment, consultation, and follow up during the period from the 1st of March to the 31st of August 2008. A written consent was obtained from each patient and was kept on file. The work was for 5 days per week with working hours of 4-5 hours/day. Two hundred forty-three patients with different congenital coagulation disorders were included through pre-coded questionnaire form. Data were collected by the researcher only by direct interviewing with the patients or their parents or close relative. Data such as age of onset of symptom, age at diagnosis, sites of bleeding were collected. Some information were also taken from the file of the patients such as type of CCD, blood levels of factor VIII, and factor IX for hemophilic patients. Physical examination includes the site of bleeding on presentation and joint limitation. Inclusion criteria were: all patients of all age groups and from both gender who attended the center during the study period. Exclusion criteria are those hemophilic patients with AIDS who usually transferred to Al-Towaitha hospital for treatment.

Data analysis was carried out using descriptive measures including mean, median, standard deviation, percentages, and test of significant was carried out using the Chi-square test. $P \leq 0.05$ was considered significant.

Results. Hemophilia (A and B) and Von Willebrand disease constituted 90.1% of patients, rare bleeding disorders (RBD) including factor I, V, VII, X, and XIII deficiencies constituted 9.9% of the study sample. The proportion of cases with hemophilia A-B was 4:1 (**Table 1**). It was found that most patients (82.7%) had their onset of symptoms during the first year of life, and 42.8% had their onset of symptoms during the first 6 months of life. Only 1.4% had their onset of symptoms at ≥10 years. While diagnoses were obtained in 99.2% of patients after onset of symptoms; 2 patients (0.8%)

Table 1 - Distribution of the study sample according to different types of congenital coagulation disorder (CCD).

Type of CCDs	Number of patient (%)	
Hemophilia A	157	(64.6)
Hemophilia B	39	(16.0)
Von Willebrand disease	23	(9.5)
Factor 1 deficiency	6	(2.5)
Factor V deficiency	1	(0.4)
Factor VII deficiency	9	(3.7)
Factor X deficiency	3	(1.2)
Factor XIII deficiency	5	(2.1)
Total	**243**	**(100.0)**

Table 2 - Age at onset of symptoms and time of diagnosis in patients with congenital coagulation disorders (CCDS) (N=243).

Age at onset of symptom	N	(%)	Diagnosis before symptom started n (%)		Diagnosis after symptom started n (%)	
≤1 months	39	(16.0)	-	-	141	(58.5)
>1 - <6 months	65	(26.8)	-	-	40	(16.6)
6-12 months	97	(39.9)	-	-	21	(8.7)
1-2 years	21	(8.7)	-	-	12	(5.0)
3-5 years	12	(4.9)	-	-	14	(5.8)
>5 years	9	(3.7)	-	-	13	(5.4)
Total	**243**	**(100)**	**2**	**(0.8)**	**241**	**(99.2)**

were diagnosed before onset of symptoms. Generally, more than half of patients (58%) were diagnosed within one month after onset of symptoms, 83.1% within one year after onset of symptoms, and only 5.4% in more than 5 years after onset of symptoms (**Table 2**). The first bleeding site was found to have cutaneous in more than half (54.3%) of patients, and this finding was true even for hemophilic patients. The remaining (45.7%) patients had bleeding site as the following: from the mucous membrane (20.2%), circumcision (9.9%), intra-articular (5.8%), umbilical (4.1%), and intramuscular (2.9%). Tooth extraction (0.8%) and other sites (from ear, intracranial hemorrhage, and postoperative) in 2% of patients (**Table 3**). 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 patients (**Table 4**).

For patients with targeted joint involvement (hemarthrosis), 38.3% of them were found to have only one targeted joint, 36.7% had 2 targeted joints, and 25% had 3 or more targeted joints, which was observed in hemophilia, factor VII, and factor X deficiencies, 2 or more targeted joints were found in 37.6% and 43.6% of patients with hemophilia A and hemophilia B respectively (**Table 5**).

Of 106 patients with joints limitation, 47.2% of them had limitation in one joint, 28.3% had limitation in 2 joints, and 24.5% had limitation in 3 or more joints. Hemophiliacs corresponded to 96.2% of all patients who had limitation in joints movement. Limitation in 3 or more joints was found in patients with hemophilia A, hemophilia B, and patients with factor X deficiency. Of all patients with congenital coagulation disorders, 16.9% had limitation in both knee joints, which was observed in patients with hemophilia A, hemophilia B, factor X deficiency, and patients with factor VII deficiency. Limitation in both elbows or both ankles was not observed in any disease except hemophilia A (**Table 6**).

Discussion. During the study period, the researcher did not encounter any difficulties in interviewing the patients or examining them, on the contrary they were very cooperative particularly when they describe

Table 4 - Degree of severity of hemophilic patients in the studied sample.

Degree of severity	Hemophilia A n (%)	Hemophilia B n (%)	Total n (%)
Mild	17 (10. 8)	5 (12. 8)	**22 (11. 2)**
Moderate	38 (24. 2)	6 (15. 4)	**44 (22. 5)**
Severe	102 (65.0)	28 (71. 8)	**130 (66. 3)**
Total	157	39	**196**

x^2 = 1.41, decree of freedom =2, p=0.494

Table 3 - First bleeding site in patients with congenital coagulation disorders.

First site of bleeding	Hemophilia A	Hemophilia B	Von Willebrand disease[4]	Rare congenital coagulation disorders	Total n (%)
Cutaneous	90	24	9	9	**132 (54.3)**
Mucous membrane	26	7	8	8	**49 (20.2)**
Circumcision	18	2	3	1	**24 (9.9)**
Intra-articular	10	4	-	-	**14 (5.8)**
Umbilical	6	-	1	3	**10 (4.1)**
Intra-muscular	4	1	2	-	**7 (2.9)**
Tooth extraction	2	-	-	-	**2 (0.8)**
Other sites	1*	1†	-	3	**5 (2.0)**
Total	**157**	**39**	**23**	**24**	**243 (100)**

*from ear, †PO - postoperative, ‡ICH - intracranial hemorrhage

Table 5 - Number of targeted joints in those patients who had a positively joint involvement in the studied sample.

Number of targeted joints	Hemophilia A	Hemophilia B	Von Willebrand disease	Factor I deficiency	Factor VII deficiency	Factor X deficiency	Total
One joint	40 (25. 5)	7 (17. 9)	1	1	-	-	**49 (38. 3)**
Two joints	36 (22. 9)	10 (25. 6)	-	-	-	1	**47 (36. 7)**
Three or more joints	23 (14. 6)	7 (17. 9)	-	-	1	1	**32 (25.0)**
Total	99	24	1	1	1	2	**128**

Table 6 - Distribution of limitation in joint movement in those patient who had a positively joint limitation in the studied sample.

Joints limitation	Hemophilia A		Hemophilia B		V0n Willebrand disease		Factor VII deficiency		Factor X deficiency		Total	
One joint	41	(26.1)	7	(18)	1	(4.3)	1	(11.1)	-	-	**50**	**(47.2)**
Two joints	23	(14.7)	6	(15.4)	-	-	1	(11.1)	-	-	**30**	**(28.3)**
Three or more joints	20	(12.7)	5	(12.8)	-	-	-	-	1	(33.3)	**26**	**(24.5)**
Total	**84**		**18**		**1**		**2**		**1**		**106**	
Both knees	31	(19.8)	8	(20.5)	-	-	1	(11.1)	1	(33.3)	**41**	**(16.9)**
Both elbows	14	(8.9)	-	-	-	-	-	-	-	-	**14**	**(5.8)**
Both ankles	1	(0. 6)	-	-	-	-	-	-	-	-	**1**	**(0.4)**
Total	**46**		**8**		-	-	**1**		**1**		**56**	

their difficulties in getting to the center or obtaining treatment, and they made demand from the researcher to forward their needs to the government and to the Ministry of Health to improve the level of services that they are obtaining. In this study, 90.1% of patients had either hemophilia or Von Willebrand disease and this result is similar to the studies from Iraq,[4] Kingdom of Saudi Arabia (KSA),[5] Iran,[6] Poland,[7] Pakistan,[8] Brazil,[9] Europe,[10] and Thailand,[11] While rare congenital bleeding disorders constitute 9.9% of the studied sample and similar to the studies from Iraq[9] (11.3%), Iran,[6] (9.1%), KSA,[5] (14.3%), India,[12] (12.5%), and Pakistan,[8] (5.9%), but more than studies from Europe,[10] (3-5%), Brazil,[9] (2.4%) and Thailand,[11] (3.86%). This discrepancy is most likely due to the high rate of consanguinity marriages and large number of births per family in Iraq. The age of onset of symptoms was more prevalent (39.9%) in patients when they were at 6-12 months old. This may be explained that the child in this age begins to crawl and walk and that mobility causes the initiation of easy bruising, intramuscular hematomas, and hemarthrosis which were noticed in patients with hemophilia, Von Willebrand disease, factor VII, and factor X deficiencies.

Within one month after onset of symptoms, diagnosis establishment was the highest prevalence (58%) due to severe form of the disease, high awareness of the patient's family (occurrence of the disease in older child or the present of family history), or accurate diagnosis. While those who had delayed in diagnosis for more than one months after onset of symptoms: patients either had mild disease with infrequent bleeding, careless of the patient's family, no family history of the disease, or misdiagnosis. Unfortunately, no other studies were evaluated for comparison.

As the first bleeding site, cutaneous bleeding was the most prevalent (54.32%) This is due to the onset of symptoms occurred mostly when the child begins to crawl and walk causing bruising. Unfortunately, no other studies were accessed for comparison. Intra-articular bleeding was the more prevalent site (52.7%) due to the high proportion of hemophiliacs who usually presented with hemarthrosis.

Most patients (96.1%) who had ≥1 targeted joints were hemophiliacs, but no targeted joints were observed in factor V or factor XIII deficiencies. Also, the majority (96.2%) of those patients with joint limitation were hemophiliacs. Sometimes, factor VII, factor X, and Von Willebrand disease mimicked hemophilia in targeting joints and causing joint limitation.

There is a clear need for extensive study to determine the exact prevalence and incidence of congenital coagulation disorders. Also, the need to provide governmental and social supports, financial funding, adequate medical and surgical care, and wheel chairs for those who need them. With the need for instituting new and efficient centers in governorates other than Baghdad city.

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