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Magnitude of arthropathy in patients with hemophilia: A single-center experience

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Abstract:

BACKGROUND: Hemophilia is a sex-linked bleeding disorder. Affected patients suffer spontaneous or post-traumatic bleeding into various sites of the body, mainly into joints, depending on the level of coagulation factor deficiency.

AIMS: This descriptive study is designed to assess the prevalence and extent of arthropathy and evaluate the functional status of hemophiliacs in Erbil, Northern Iraq.

SETTINGS AND DESIGN: A descriptive study of all registered hemophiliacs at Nanakali Hemato-Oncology Teaching Centre, Erbil, Iraq.

PATIENTS AND METHODS: Over 15 months (October 2015 to February 2017), a total of 133 hemophilia patients were studied. Their hospital records were used to retrieve clinical and laboratory data, mainly their coagulation profile. All patients were clinically examined at the daycare center; plain radiography was used to evaluate the degree of joint damage based on Petterson score. The magnitude of joint disease was assessed, and patients' functional status was evaluated depending on Functional Independence Score in Hemophilia (FISH).

STATISTICAL ANALYSIS USED: Statistical analysis used MS Excel 2010.

RESULTS: Hemophiliacs mean age was 12.9 years. Patients with severe hemophilia presented earlier and had more bleeding episodes. At least one bout of hemarthrosis was recorded in 103/133 patients during the course of their disease with knee joint most frequently involved (in eighty patients) followed by elbow, ankle, wrist, and shoulder. The Petterson score related significantly to age of the patient, number of bleeds, and severity of hemophilia. Majority, 67%, of hemophiliacs found to have the limitation of movement. FISH score significantly related with factor activity level. Functional disability was encountered in 9.7% of cases; majority had severe hemophilia.

CONCLUSIONS: The incidence and severity of joint bleeding and functional disability were high. The FISH and Pettersson scoring systems are very useful tools in assessing patients with hemophilic arthropathy.

Keywords:

Arthropathy, Erbil, hemarthrosis, hemophilia, Iraq, limitation of movement

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Introduction

Hemophilia is a sex-linked recessive bleeding disorder mainly affecting male through female carrier. It results from a congenital deficiency in blood coagulation factors. Two types of hemophilia A and B result from deficiency of factors VIII and IX, respectively.[1] They are estimated to occur, respectively, in approximately 1 of every 5000 and 1 of every 30,000 male births worldwide. No community is immune to hemophilia as almost a third of all patients are due to fresh mutations, with negative family history.[2,3] Hemophilia is characterized by abnormal and recurrent bleeding occurs in various parts of the body but mainly into joints.[4] The clinical severity of bleeding in hemophilia is variable but correlate with the plasma factor level. Both hemophilia A and

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B are clinically classified into mild, moderate, and severe according to factor level in the plasma. Mild hemophilia is when factor concentration ranges between 5%–40% of the normal, moderate is 1%–5%, and severe hemophilia when factor level is ≤1%.[2,3] Bleeding into joints is very painful, it accounts for approximately 80% of bleeding episodes in severely affected patients with hemophilia. Recurrent hemarthroses result in the development of hemophilic arthropathy, which is the most common cause of morbidity in patients with hemophilia and greatly affects their quality of life.[5,6] Bleeding into the joint space causes adverse changes in both articular cartilage and the synovial tissue; both synovitis and cartilage changes affect each other.[7] Recurrent joint bleedings will latter cause the enlargement of the epiphysis and growth disturbance in hemophilic patients; moreover, subchondral changes may occur in the form of osteoporosis, subchondral cyst formations, and both erosions and osteophyte formation. Advance stage of arthropathy, mainly seen among severe cases, is characterized by ankylosis, fusion of the bones, similar to what happens in severe osteoarthritis.[8,9] The Pettersson score is a detailed radiologic classification of hemophilic joints that has been adopted by the World Federation of Hemophilia. It estimates the degree of joint destruction radiologically.[10]

Functional Independence Score in Hemophilia (FISH) is a tool for assessing hemophiliacs' functional status and degree of limitation of their movement. FISH is a performance-based instrument used to objectively assess musculoskeletal function of patients with hemophilia. FISH evaluates the degree of limitation of movement (LOM) through measuring the patient's independence in performing seven activities under three categories: self-care (grooming and eating, bathing, and dressing), transfers (chair and floor), and mobility (walking and step climbing).[11]

The aim of the present work was to evaluate the severity of arthropathy, clinically and radiologically, and to functionally assess hemophiliacs attending our daycare center where patients receive the substandard quality of care.

Patients and Methods

Over a period of 15 months, 133 hemophilia patients who are registered at Nanakali Hemato-oncology Teaching Centre in Erbil, Northern Iraq, were conveniently recruited and studied mainly for arthropathic complications related to their disease. The study was explained to the enrollees and informed consent was obtained from patients or patients' guardian. The experimental protocol was approved by the Ethical Committee of the College of Medicine, Hawler Medical University.

Full history of the disease was taken at the hemophilia daycare clinic within the center; hospital records were used to retrieve laboratory and clinical data including personal information, age of diagnosis, family history, type of hemophilia, clinical presentations, sites, and frequency of bleeding. The percentage of coagulation factor deficiency at the time of diagnosis was used to classify hemophiliacs into mild, moderate, and severe. Clinical examination of the involved joints was done; the degree of LOM and functional status among hemophiliacs was evaluated based on the FISH.[11] To assess the degree of joints destruction, all patients were arranged to have conventional frontal and lateral radiography for the target joint, which was scored according to the Pettersson score by a radiologist.[10,12]

All patients had relevant hematological tests of complete blood counts, bleeding time, and coagulation tests. Prothrombin time, activated partial thromboplastin time, factor VIII, and factor IX assays were carried out using coagulometer (Stago, France). Data were statistically analyzed using Microsoft® Excel, Professional Edition 2010. Qualitative data were described in number and percentage. Quantitative data were described using mean, standard deviation median, and range. Chi-square test was used to compare categorical data. Kruskal–Wallis test was used to compare more than two sets of numerical data. Correlations between two quantitative variables were assessed using Spearman's coefficient. Significance was considered at $P < 0.05$.

Results

In this study, 118 patients (89%) with hemophilia A and 15 patients (11%) with hemophilia B were recruited. Their ages ranged between 9 months and 51 years with mean age of 12.9 (±9.7) years. More than 82% were below 20 years, of whom two-third were below 10 and only two patients aged >40 years. Patients suffering severe hemophilia constituted 31.6% (42 patients); those with moderate disease were 45 (33.8%) and the remaining 46 patients (34.6%) had mild disease [Table 1].

It was found that 34 patients (26%) had spontaneously bleeding, 68 (51%) bled after minor trauma, and 31 patients (23%) had bleeding only after major trauma. Majority of severe hemophiliacs bled spontaneously, whereas most mild cases bled only after major trauma. The annual frequency of bleedings related significantly to levels of factor deficiency. The average number of bleeds per year was 4.2, 5.4, and 7.4, among mild, moderate, and severe hemophiliacs, respectively. Patients with severe hemophilia had more attacks of bleeding than mild cases within a specified period. Both severity and annual frequency of bleeding significantly related to severity of factor deficiency ($P < 0.05$) [Table 2].

Table 1: Age and some clinical characteristics of the hemophiliacs

Characteristic	*n* (%)
Age (years)	
0-10	62 (46.5)
11-20	48 (36)
21-30	16 (12)
31-51	7 (5.5)
Hemophilia	
A	118 (89)
B	15 (11)
Severity	
Mild	46 (34.6)
Moderate	45 (33.8)
Severe	42 (31.6)
Joint deformities (*n*=55; 41%)	
Mild H.	0/46
Moderate H.	20/45
Severe H.	35/42

Table 2: Frequency and severity of bleeding versus disease severity

	Disease severity			*P**
	Mild (*n*=46)	Moderate (*n*=45)	Severe (*n*=42)	
Type of bleeding				
Spontaneous (*n*=34)	0	5	29	<0.001
Minor trauma (*n*=68)	15	40	13	
Major trauma (*n*=31)	31	0	0	
Bleedings per year				
Range	2-6	2-9	3-10	<0.001
Mean±SD	4.2±1	5.4±1.6	7.4±1.9	
Median	4	5	8	

*Kruskal-Wallis test; statistically significant at $P \leq 0.05$. SD=Standard deviation

The current study demonstrated that 31 patients (23.3%) had bleeding into joints only. Smaller numbers had bleedings only into soft tissues or mucus membranes, whereas more than half had mixed type bleedings into joints, mucus membranes, and soft tissues [Figure 1]. In this series, about 76% of patients had got hemarthrosis during the course of their disease with joints most frequently affected being the main load or strain-bearing articulations. Bleeding into knee joint alone was recorded in 42 patients; 38 others had bleedings into knee and other joints. Elbow was affected in 11 patients, ankle in 6, wrist in 4, and shoulder joint in 2 patients.

Joint misalignment and deformities were present in 55 hemophiliacs (41%), whereas the remaining 78 patients did not have any deformity. Deformities of knee recorded in 35 patients, elbow in 6, ankle in 4, and multiple joint deformities found in 10 patients. Majority (83%) of hemophiliacs with severe disease had joint deformities, whereas none with mild disease had any deformity [Table 1].

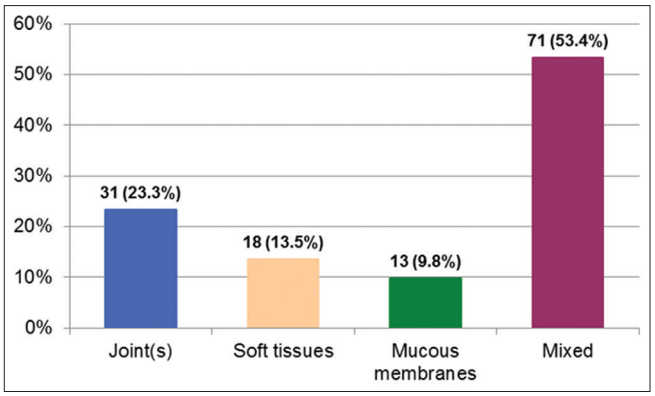

Figure 1: Sites of bleeding

As illustrated in Table 3, the mean Pettersson score among hemophiliacs in the current series was 5.3; there was a significant negative relation between factor activity level and Pettersson score ($P < 0.001$). The degree of LOM, represented by FISH, among the studied set of hemophiliacs was variable; the mean FISH was 28, ranged from 17 to 34. The FISH score related positively with factor activity level ($P = 0.01$); the score was highest in patients with mild hemophilia with a mean of 29.5 ± 2.4 and lowest among those with severe hemophilia, with a mean of 26 ± 5.3. There was a significant positive correlation between the FISH score and factor level ($r = 0.29$; $P = 0.001$) [Figure 2]. Within the studied group, 13 patients (10%) were functionally disabled because of their disease; of which ten patients had severe hemophilia and three had moderate disease [Table 3].

Discussion

Hemophilia is the second most common inherited coagulation disorder after VWD. In Nanakali Teaching Hemato-Oncology Centre, 133 male hemophiliacs are registered, this corresponds to a prevalence of 6.6/100,000 population. This figure is lower than that reported by other countries were figures as high as 20.5 and 10–15/100,000 are reported in the USA and Europe, respectively.[13,14] This lag between expected and registered numbers may be due to unavailability of tests for the diagnosis in most of the hospitals and a low number of specialized hemophilia center leading to the fact that patients are being scattered over many unspecialized hospitals.

In this series, 89% of the patients had hemophilia A and 11% hemophilia B. This is widely accepted as hemophilia A accounts for about 85% and hemophilia B for about 15% of all hemophilia cases.[2] Patients aged ≤10 years constituted 46.5%; the next commonly affected age group was 11–20 years (36%). This distribution is identical with findings of Al-Murshidi in Baghdad.[15] The relative rarity

Table 3: Relationship between Petterson score, functional independence score in hemophilia score, and the factor activity level among hemophilic patients

	Factor level			*P**
	Mild (*n*=46)	Moderate (*n*=45)‡	Severe (*n*=42)†	
Petterson score				
Range	0-9	0-11	1-12	<0.001
Mean±SD	4.3±2.8	5±3.1	6.9±3.3	
Median	5	4	8	
FISH score				
Range	25-33	19-33	17-34	0.01
Mean±SD	29.5±2.4	28.3±3.8	26±5.3	
Median	30	29	26	

*Kruskal-Wallis test; statistically significant at $P \leq 0.05$, †Ten of them were functionally disabled, ‡Three of them were functionally disabled. SD=Standard deviation, FISH=Functional independence score in hemophilia

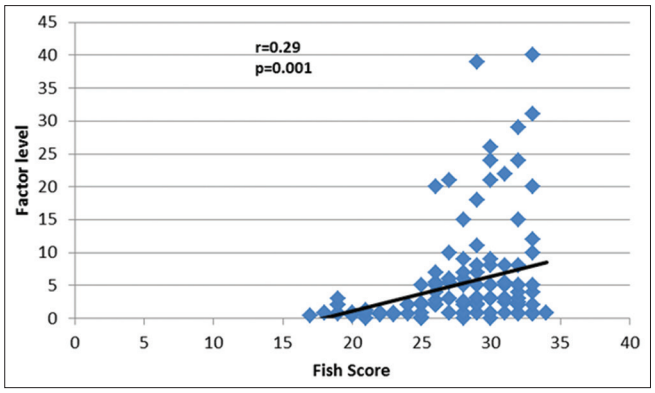

Figure 2: Correlation between Functional Independence Score in Hemophilia and factor level

of older hemophiliacs in our locality can be explained as many mild cases remain undiagnosed, and many others with severe diseases die early due to inadequate management. This is unlike the situation in the west where prophylactic replacement therapy turns young hemophiliacs to live almost normal life.[16]

In this series, severe hemophiliacs represented less than one-third of all patients. This is a bit different than the case in the Western world as many reports reveal that severe cases constitute the major portion because of frequent attending to hospitals due to repeated bleeding episodes and early diagnosis. The possible explanation for this is migration seeking better care and/or early death of severe cases because of inadequate care.

Severe hemophiliacs had more attacks of hemarthrosis; the annual frequency of bleeding significantly related to the severity of factor deficiency ($P < 0.05$). Most of the spontaneous bleeders had severe disease, and some had moderate hemophilia, whereas none with mild hemophilia ever had a spontaneous bleeding episode. Similar results by Al-Murshidy who reported that episodes of spontaneous hemarthrosis were infrequent in moderate and absent in mild hemophilia, and major trauma or surgery being important for the detection of mild hemophilia.[15]

The overall incidence of hemarthrosis was more than 75%. Knees were most frequently affected either alone or together with other joints, followed by elbows then ankles, wrists, and shoulders. The frequency and site distribution of joint bleeding is comparable to many other reports.[15,17,18]

Deformities of joints were recorded in 41%. The frequency and site of deformed joints followed the rate of affection by hemarthrosis. There was a statistically significant negative correlation ($P = 0.03$) between the severity of joint disease represented by Petterson score and factor activity level [Figure 3a]. The most frequently observed arthropathic changes were enlargement of epiphysis and irregular subchondral surface, seen in 36% and 34% of hemophiliacs, respectively; osteoporosis, however, was observed in 16%. It was found that the Petterson score positively correlated with both age of the patient and bleeding frequency, represented by a number of bleeds per year [Figure 3b and c]. These findings are in agreement with Fischer *et al*.,[19] who reported that the Pettersson score increases by one point for every three joint hemorrhages occurring after 5 years of age and Van Dijk *et al*.,[20] who assessed joint damage using Pettersson score based on age groups in severe hemophiliacs and reported that the score increased with the cumulative number of joint bleeds.

Deformities of joints from hemarthrosis resulted in a variable degree of LOM depending on the degree and number of joint affection. The LOM was assessed depending on FISH. In this cohort, out of 55 patients with joint deformities, 35 had severe hemophilia, of them ten had multiple joint deformities. FISH score was significantly higher in those with mild hemophilia than in patients with moderate-or-severe hemophilia. This finding is consistent with results of Gurcay *et al*.,[21] who reported that about 50% of severe hemophilia patient develop joint deformities with a high potential for functional disability if prompt treatment is unavailable or inadequate. The degree of LOM in our hemophiliacs is higher comparing to figures reported from developed countries where better treatment and care is provided; however, it is quite similar to results reported from developing part of the world, where as, in our center, hemophiliacs receive only on demand therapy.[22,23] In the current series, there were 13 patients (10%) who had severe functional disability and could not move without aid, their mean FISH was 20, of whom ten had severe and three had moderate hemophilia. Among functionally disabled patients, six were ≤15 years and they were not attending school due to their disability, and the other seven were older and completely dependent.

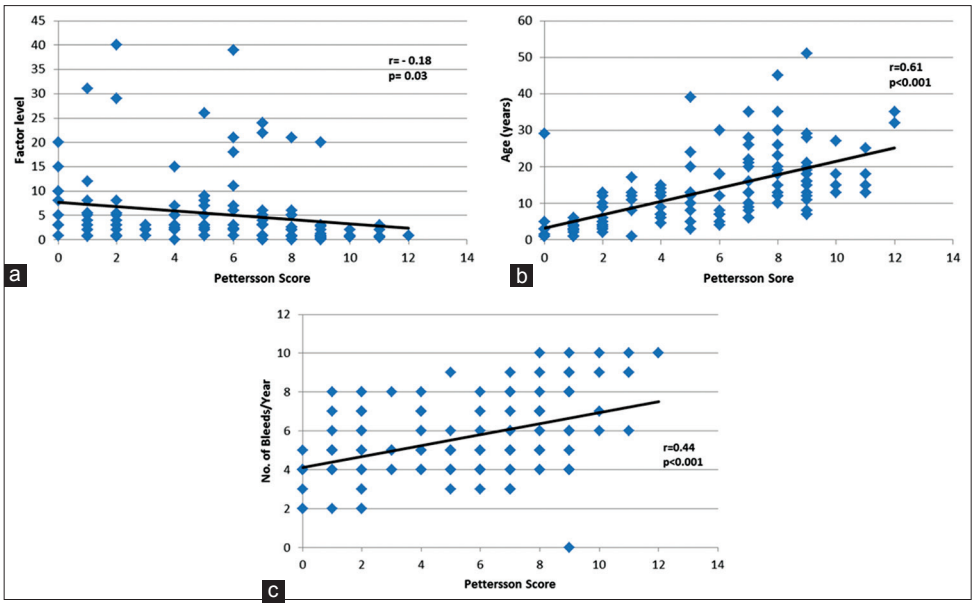

Figure 3: Correlation between the Pettersson score and (a) factor activity level, (b) age, and (c) number of bleeds/year

In conclusion, relatively high incidences of joint bleedings, joint deformity, and variable degree of LOM were recorded among hemophiliacs in our locality. The severity of joint affection represented by Petterson score was significant and related to age, frequency of bleedings, and severity of hemophilia. A good proportion of patients suffered severe functional disability. This reflects the inadequate medical services, and poor quality of rehabilitation care our hemophiliacs received.

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Conflicts of interest
There are no conflicts of interest.

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