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 Pettersson 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 Pettersson 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

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
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%. 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].
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].

**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**

| Type of bleeding | Mild ($n=46$) | Moderate ($n=45$) | Severe ($n=42$) | $P*$ |
|------------------|---------------|-------------------|-----------------|------|
| Spontaneous      | 0             | 5                 | 29              | <0.001 |
| Minor trauma     | 15            | 40                | 13              |       |
| Major trauma     | 31            | 0                 | 0               |       |
| Bleedings per year | 2.6±1       | 2.9±1.6           | 3.10±1.9        | <0.001 |

As indicated above, 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 hemorrhosis 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].

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 of severe hemophilia is supported by a high proportion of patients with mild disease (34.6%) and moderate disease (33.8%) and a low rate of severe disease (31.6%).

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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 hemorrhosis; 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.\[13\]

The overall incidence of hemorrhosis 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 hemorrhosis. 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 hemorrhosis 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.

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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 Pettersson 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.

References
1. Roberst HR, Ma AD. Overview of inherited haemorrhagic disorders. In: Colman RW, Marder VJ, Clowes AW, George JN, Goldhaber SZ, editors. Haemostasis and Clinical Practice. 5th ed. PA, USA: Lippincott Williams & Wilkins; 2006. p. 877-85.
2. Stonebraker JS, Bolton-Maggs PH, Soucie JM, Walker I, Brooker M. A study of variations in the reported haemophilia A prevalence around the world. Haemophilia 2010;16:20-32.
3. Franchini M, Favaloro EJ, Lippi G. Mild hemophilia A. J Thromb Haemost 2010;8:421-32.
4. Ozkan S, Turkatas U, Ceylan FM, Guner S, Dogan A, Hiz O. Clinical evaluation of the joints of patients with hemophilia A. Arch Clin Exp Surg 2014;3:233-9.
5. Carcao MD, van den Berg HM, Ljung R, Mancuso ME, PedNet and the Rodin Study Group. Correlation between phenotype and genotype in a large unselected cohort of children with severe hemophilia A. Blood 2013;121:3946-52, S1.
6. Rodriguez-Merchan EC. Aspects of current management: Orthopaedic surgery in haemophilia. Haemophilia 2012;18:8-16.
7. Roosendaal G, Lefeber F. Prophylactic treatment for prevention of joint disease in hemophilia – Cost versus benefit. N Engl J Med 2007;357:603-5.
8. Jansen NW, Roosendaal G, Lafeber FP. Understanding haemophilic arthropathy: An exploration of current open issues. Br J Haematol 2008;143:632-40.
9. Jacobson JA, Girish G, Jiang Y, Sabb BJ. Radiographic evaluation of arthritis: Degenerative joint disease and variations. Radiology 2008;248:737-47.
10. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. Clin Orthop Relat Res 1980;149:153-9.
11. Poonnoose PM, Thomas R, Keshava SN, Padankatti S, Pazani D, et al. Psychometric analysis of the Functional Independence Score in Haemophilia (FISH). Haemophilia 2007;13:620-6.
12. Pergantou H, Matsinos G, Platokouki H, Papadopoulos A, Aronis S. An attempt to improve the clinical scale for assessment of haemophilic arthropathy in children. J Pediatr Orthop B 2009;18:204-10.
13. Qui Y, Nie X, Yang Z, Yin H, Pang Y, Dong P, et al. The prevalence of hemophilia in mainland China: A systematic review and meta-analysis. Southeast Asian J Trop Med Public Health 2014;45:455-66.
14. Peyvandi F, Bolton-Maggs PH, Batorova A, De Moerloose P. Rare bleeding disorders. Haemophilia 2012;18 Suppl 4:148-53.
15. Al-Murshidy KW. Clinico-Pathological Study of Hemophilia in Baghdad. FIBM-Path. Baghdad, Iraq: Iraqi Board for Medical Specialties; 2000.
16. Canaro M, Goranova-Marinova V, Berntorp E. The ageing patient with haemophilia. Eur J Haematol 2015;94 Suppl 77:17-22.
17. Bakan B, Canbal M. Hemofilik artropati ve rehabilitasyonu. Yeni Tip Dergisi 2014;31:78.
18. Rodriguez-Merchan EC. Musculoskeletal manifestations of haemophilia. Blood Rev 2016;30:333-410.
19. Fischer K, van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, de Kleijn P, et al. The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia. Blood 2002;99:2337-41.
20. van Dijk K, Fischer K, van der Bom JG, Grobbee DE, van den Berg HM. Variability in clinical phenotype of severe haemophilia: The role of the first joint bleed. Haemophilia 2005;11:438-43.
21. Gurcay E, Eksioglu E, Ezer U, Tuncay R, Cakci A. Functional disability in children with hemophilic arthropathy. Rheumatol Int 2006;26:1031-5.

22. Hassan TH, Badr MA, El-Gerby KM. Correlation between musculoskeletal function and radiological joint scores in haemophilia A adolescents. Haemophilia 2011;17:920-5.

23. Tlacuilo-Parra A, Villela-Rodriguez J, Garibaldi-Covarrubias R, Soto-Padilla J, Orozco-Alcala J. Functional independence score in hemophilia: A cross-sectional study assessment of Mexican children. Pediatr Blood Cancer 2010;54:394-7.