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MUSCULOSKELETAL MANIFESTATIONS IN HEMOPHILIC PATIENTS IN IBN-SINA TEACHING HOSPITAL, IN MOSUL CITY. IRAQ. 2020

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ABSTRACT

Background: Hemophilia is a coagulation disorder caused by a deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B, also known as Christmas disease). Hemophilic patients can experience numerous musculoskeletal complications. **Objectives:** Evaluation of musculoskeletal manifestations in hemophilic patients, including clinical and radiological characteristics, and the correlation between them. **Patients and Methods:** A case series study was conducted on fifty male hemophilic patients aged between 4 and 50 years with moderate and severe hemophilia. The study took place in the hematology unit of Ibn-Sina teaching hospital over six months from October 2020 to March 2021. All patients underwent a thorough history taking and local physical examination of the 'target joint' using the Gilbert score. Additionally, all patients received conventional frontal and lateral radiography of the target joint at the radiology institute. **Results:** Chronic synovitis was present in 32 patients, acute hemarthrosis in 20 patients, deforming arthropathy in 6 patients, muscle bleeding in 5 patients, and pseudotumor in one patient. A statistically significant positive correlation was found between Gilbert's score and Pettersson's score. **Conclusion:** Hemophiliac patients often experience musculoskeletal complications, such as chronic synovitis, acute hemarthrosis, deforming arthropathy, muscle bleeding, and pseudotumor. The knee is the most commonly affected joint. The evaluation of joint status is crucial and can be done using the Gilbert score and Pettersson scoring system.

KEYWORDS: Arthropathy, Gilbert Score, Hemophilia, Musculoskeletal Manifestations, Pettersson Score, Synovitis.

INTRODUCTION

Hemophilia is a common X-linked recessive coagulation disorder caused by abnormalities in coagulation proteins, specifically factor VIII (FVIII) and factor IX (FIX). Hemophilia A, also known as classic hemophilia, results from a deficiency in FVIII, while hemophilia B, or Christmas sickness, is caused by a deficiency in factor IX.[1] Hemophilia A and B are the most common single coagulation factor deficiencies, although inherited deficiencies of other coagulation factors also occur.[2]

It is estimated that hemophilia A occurs in 1 out of every 5,000 to 10,000 live male births, while hemophilia B is approximately one-fifth as common. There is no specific racial predilection.[3,4]

Based on the patient's residual FVIII and FIX blood concentrations (1 IU/dL = 1%), hemophilia is graded as severe hemophilia: <1%; moderate hemophilia: ≥1–5%; mild hemophilia: ≥6–40%.[1,5]

Hemophilia is a condition characterized by spontaneous bleeding into the joints, leading to arthritis deformities. The ankles, knees, and elbows are the most frequently affected joints.[6,7] Hemophilic arthropathy is the main health issue for individuals with severe hemophilia A and B, resulting from repeated bleeding inside the joints. Muscle bleeding is the next most common type of bleeding in patients with hemophilia, usually caused by direct impacts or sudden strains. If muscle bleeding continues without being resolved or if there is progressive bleeding beneath the periosteum, it can lead to painless, expanding hematomas that become encapsulated and calcified over time.[8,9]

The development of hemophilic arthropathy involves the combination of inflammatory and degenerative processes along with iron deposition. Hemophilic arthropathy is identified by two main characteristics: cartilage breakdown and persistent synovitis. After a hemorrhage, the synovium plays a crucial role in absorbing blood from the joint. However, as time passes, hemosiderin accumulates in the synovial tissue, leading to synovial hypertrophy, chronic inflammation, and the generation of synovial fibroblast DNA and synovial cell proliferation. The neovascularization seen in chronic synovitis is also affected by iron buildup, local cellular stress due to lack of oxygen, and proinflammatory mediators. This results in inflamed, fragile tissue that is more susceptible to bleeding. Therefore, continuous bleeding from minor injuries establishes a harmful cycle.[10,11]

The current study aimed to assess musculoskeletal manifestations in hemophilia A and B, focusing on clinical and radiological characteristics.

PATIENTS AND METHODS

Study Setting and Design: A case series study was conducted in the hematology unit of Ibn-Sina Teaching Hospital within a period of six months, from October 2020 to March 2021, after obtaining approval for the study protocol from the College of Medicine, University of Mosul. The study included fifty male hemophilic patients with moderate and severe hemophilia, aged between 4 and 50 years. Patients with mild hemophilia were excluded from the study.

Data collection: All patients underwent a thorough history taking and a physical examination of the specific joint being studied. We collected data through face-to-face interviews with each participant, using questionnaires that included a patient approval form to participate in the research. The questionnaires also covered socio-demographic information such as name, age, residence, family history, and age at the time of diagnosis. Additionally, we collected medical parameters such as blood group, Rh group, hemophilia severity, and the number of bleeding episodes. The musculoskeletal parameters included pain frequency (during movement, continuous, or during bleeds), pain location, triggering factors (bleeding episodes, movement), and the number and type of joints involved.[5]

Here is the revised text

A pain score of 0 indicates no discomfort, no functional impairment, and no need for analgesics except in cases of acute hemarthrosis.

1. Mild discomfort that does not interfere with daily activities or work, with occasional need for non-narcotic pain medication.
2. Moderate pain that may partially or completely disrupt work or daily activities, requiring non-narcotic medication and possibly occasional use of narcotics.
3. Often requiring both non-narcotic and narcotic drugs, severe pain that interferes significantly with work or daily activities (ADL).[12]

Examination of target joint: The Gilbert score is a physical examination scale developed by the World Federation of Hemophilia (WFH) to assess the condition of joints such as knees, ankles, elbows, and hips. It evaluates the presence of swelling, atrophy, crepitus, flexion contractures, loss of range of motion, axial deformities, and instability. The score ranges from 0 to 12, with 0 indicating normal and 12 indicating the most severe impact.[13,14] The study examined the presence of swelling, muscle atrophy, crepitus, flexion contracture, and axial deformity in the knee joint. The center of the knee joint usually aligns with a line connecting the hip and ankle joints. However, individuals with genu varum (bowleg deformity) have the center falling to the lateral side of the axis connecting the hip and ankle joints, while genu valgum (knock-knee deformity) occurs when the center is medial to the lower extremity's biomechanical axis. Axial deformity was assessed by measuring the deviation from a reference line. Furthermore, knee joint stability was evaluated using anterior and posterior drawer tests, medial and lateral collateral ligament stress tests, and ankle anterior drawer tests.[15]

All patients underwent traditional frontal and lateral X-rays of the specific joint using the Carestream DR (ASCEND QS-550) radiology device at the radiology institute. A single radiologist evaluated all the X-rays and scored them based on the Pettersson score, which is the recommended radiological classification by the Orthopaedic Advisory Committee of the WFH. The possible joint score ranged from 0 to 13.[16,17]

Statistical analysis: The data was entered into a computer using the Microsoft Excel program, and analysis was conducted using the software Minitab version 18 for Windows. The mean and standard deviation were used to express the numerical data. The Chi-square ($\chi 2$) test was used to evaluate musculoskeletal manifestations in hemophilia A and B. The P-value was considered significant when it was less than 0.05.

RESULTS

In the present study, 50 hemophilic patients were enrolled, with a mean age of 20.2 ± 11.5 years. The age range at the time of diagnosis was 1.0 to 12.0 years. Additional socio-demographic characteristics of hemophilic patients can be found in Table 1.

Table 1: Socio-demographic characteristics parameters.

		Mean ± SD	Range
Age (years)		20.2 ± 11.5	4.0 – 50.0
Age at time of diagnosis (years)		1.94 ± 2.10	1.0 – 12.0
		No.	**%**
Family history	Present	36	72.0
	Absent	14	28.0
Residence	Rural	27	54.0
	Urban	23	46.0
Marital status	Single	36	72.0
	Married*	14	28.0
Education	Illiterate	22	44.0
	Primary school	14	28.0
	Secondary school	12	24.0
	University +	2	4.0
Total		**50**	**100.0**

*** One divorced man.**

The distribution of Hemophilia types and their severity is shown in Figure 1. It was found that Hemophilia A was the most common type, affecting 47 patients, with severe Hemophilia present in 33 patients. Moderate and type B Hemophilia were found in 17 and 3 patients respectively.

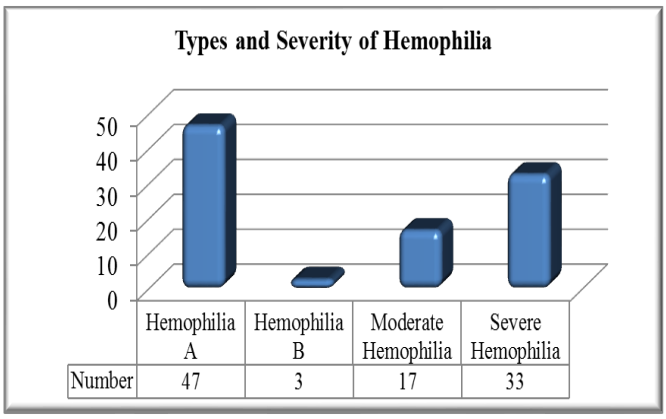

Figure 1: Distribution of Type and Severity of hemophilia.

The number of bleeding episodes per month varied among hemophiliac patients. The majority experienced pain during bleeding episodes (82.0%), while (10.0%) reported pain during movement, and (8.0%) had continuous pain, as shown in Table 2.

Table 2: The site of Bleeding and Pain.

Items		**No.**	**%**
Number of bleeding/month	0 – 1	17	34.0
	2 – 3	20	40.0
	4 – 5	12	24.0
	6 – 7	1	2.0
Pain frequency	During bleeds	41	82.0
	Continuous	4	8.0
	During movement	5	10.0
Pain triggering factors	Bleeding	42	84.0
	movement	8	16.0
Pain location	Knee	39	78.0
	Ankle	7	14.0
	Thigh	2	4.0
	Hip	1	2.0
	Elbow	1	2.0
Pain intensity	No	6	12.0

	Mild	11	22.0
	Moderate	15	30.0
	Sever	18	36.0
Total		50	100.0

The distribution of the number of involved joints is depicted in Table 3. The findings revealed that 40.0% exhibited involvement of a single joint, with the knee joint being involved in 80.0% of cases.

Table 3: The distribution of the numbers of Involved and Target joints.

Hemarthrosis		**No.**	**%**
Number of joints	1	20	40.0
	2	16	32.0
	3	7	14.0
	4	4	8.0
	5 – 7	3	6.0
Target joints [> 4-times bleeding/6 months]	Knee	40	80.0
	Ankle	7	14.0
	Hip	2	4.0
	Elbow	1	2.0
Total		50	100.0

Table 4 shows how the target joint was clinically assessed using the Gilbert score.

Table 4: The musculoskeletal examination of the target joint by Gilbert score.

		No.	**%**
Musculoskeletal examination*	Joint swelling	42	84.0
	Synovitis	29	58.0
	Muscle atrophy	15	30.0
	Axial deformity in the knee	22	44.0
	Crepitus on motion	33	66.0
Range of motion	0	23	46.0
	1	22	44.0
	2	5	10.0
	Flexion contracture	13	26.0
	Instability	3	6.0

Chronic synovitis was present in 32 patients, acute hemarthrosis was present in 20 patients, deforming arthropathy was present in only 6 patients, muscle bleeding was shown in 5 patients, and a pseudotumor was present in 1 patient.

Table 7: The musculoskeletal complications among hemophilic patients.

Musculoskeletal complications*	**No.**	**%**
Acute hemarthrosis	20	40.0
Muscle bleeding	5	10.0
Chronic Synovitis	32	64.0
Deforming arthropathy	6	12.0
Pseudotumor	1	2.0

DISCUSSION

Fifty individuals with hemophilia were assessed to determine if they faced any musculoskeletal problems. The average age of the patients was 20.2 ± 11.5, with the youngest patient being 4 years old and the oldest being 50 years old. This suggests that hemophilic patients may be living longer due to improved access to factor concentrates.[18] The age range of the individuals at the time of diagnosis was from 1 to 12 years old. The study revealed that 72.0% of patients had a positive family history of hemophilia, largely resulting from increased consanguinity in the Mosul community, while 28.0% had a negative family history due to spontaneous mutations. This finding is in line with Lateef *et al.*[19]

The study found that rural areas had a higher rate of patients (54.0%) than urban areas (46.0%), which may be due to the increasing rate of consanguineous marriage and was consistent with AL-Zubaidy.[20]

44% of the participants were illiterate because their parents refused to send them to school to prevent falling

and bleeding. 28.0% were attending primary school, 24.0% were attending secondary school, and 4.0% went to university. In Portugal, most of the participants had completed high school education or higher (74.4%).[5]

Among 50 patients, 94% had hemophilia A (47 patients), and 6% had hemophilia B (3 patients). This is consistent with the Shamoon study.[16] Patients with severe hemophilia made up 66%, while those with moderate hemophilia made up 34% this is consistent with Kadhim *et al.*[21]

"The number of bleeds per month varies among hemophilic patients. Younger people are more prone to falling than the older age group, which leads to more bleeding and makes them more susceptible to musculoskeletal complications. Therefore, older people are more vigilant about their condition to prevent bleeding, which is consistent with Soucie *et al.*[22]

When evaluating patients during bleeding episodes, it was found that 82.0% experienced pain only during the bleeding episodes. This pain is caused by blood filling the joint cavity, which increases pressure and leads to significant pain. Another 8.0% experienced continuous pain due to recurrent bleeding episodes, resulting in deforming arthropathy. Additionally, 10.0% reported pain during movement. This supports the findings of Paredes study.[5] Pain intensity varied among patients: 36% had severe pain, 30% had moderate pain, and 22% had mild pain. Additionally, 12% experienced no pain, which is consistent with Ghany et al.[23] This variation in pain intensity is expected, as the perception of pain is subjective, highly variable, and unique to each person. Each patient experiences pain differently due to differences in physical sensitivity, social and emotional factors, and how their joints are affected.[24]

Regarding the number of involved joints, the current study shows that 40.0% of patients had a single affected joint, 32.0% had 2 joints, 14% had 3 joints, 8% had 4 joints affected, 6.0% were 5-7 joints consistent Kadhim *et al.*[21]

In this study, the most commonly affected joints were the elbow in 2.0% of cases, the hip in 4.0% of cases, the ankle in 14.0% of cases, and the knee in 80.0% of cases. This finding aligns with the conclusion of Ghany et al.[23] who discovered that the two major joints—the knee and the ankle—were the most often impacted. They explained that while the hips are well-supported and bleed less frequently, the knee and ankle have a weight-bearing role, causing them to bleed more frequently. Gupta[25] discovered that the elbow was 55% more than the ankle 50%, while knees affected people 97% of the time.

Examination of the target joint revealed the following: 42 patients (84.0%) exhibited joint swelling, which could be attributed to bleeding, effusion, periarticular soft tissue mass, synovial hypertrophy, deformity, or bony enlargement. Additionally, 29 patients (58.0%) were diagnosed with synovitis based on clinical examination, as evidenced by the thickening of the joint and a spongy feel. Furthermore, 15 patients (30.0%) demonstrated muscle atrophy, 22 patients (44.0%) had an axial deformity in the knee, and 33 patients (66.0%) exhibited crepitus of motion. Limited range of motion was significantly increased in 27 patients (54.0%) with more frequent bleeding episodes, while only 13 patients (26.0%) displayed flexion contracture. Finally, instability was observed in only 3 patients (6.0%). These findings align with the research conducted by Ghany et al.[23]
Please keep the following text in mind:
In this study, a significant correlation was found between Gilbert's score and Pettersson's score. We aimed to identify complications that may arise in the target joint and clinically evaluated the joint using the Gilbert score. Our aim was supported by the positive correlation between Gilbert's and Pettersson's scores. According to a study by Ghany, the most frequently observed arthropathic changes by Pettersson score were irregular subchondral surface (38%), enlarged epiphysis (28%), and osteoporosis (16%). This in accordance with Ghany *et al.*[23]

The current study indicates a strong direct correlation between the severity of hemophilia and the number of joints affected. Patients with severe factor deficiency are more likely to experience bleeding, and multiple joints may be affected. This is consistent with Ghany et al.[23] However, there is no significant correlation between the severity of hemophilia and the number of bleeding episodes per month. This may be due to patient's understanding of the importance of avoiding movements that could cause bleeding. In Shamoon's study,[16] a significant relationship was found, indicating that hemarthrosis attacks were more common in severe hemophilia.

Limitations

1. Small sample size.
2. The study was carried out in a single centre.
3. Difficulty of patients reaching to hospital fear of Covid 19.

CONCLUSION

The most common musculoskeletal issues in people with hemophilia include acute hemarthrosis, persistent synovitis, deforming arthropathy, muscle hemorrhage, and pseudotumor. The knee was the joint most often affected. A useful way to assess the joint condition in hemophiliac patients is the Gilbert score. To predict the extent of hemophilic arthropathy, using the Pettersson scoring system to score the joints through radiography is a practical, accessible, and affordable method.

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