Hemophilic arthropathy: evaluation of clinical and radiological characteristics and disability

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Hemophilia is an inherited bleeding disorder which produces its greatest morbidity in the musculoskeletal system. Musculoskeletal complications of hemophilia include acute hemarthrosis, chronic arthritis and hemophilic arthropathy. We studied the clinical and radiological characteristics of joint involvement in hemophiliacs. Functional loss was also demonstrated. There were 25 patients with a mean age of 17; the mean coagulant factor level was 4.2 percent. All the patients had hemarthrotic attacks. Knees were the most commonly affected joints followed by elbows, ankles and hips. The mean number of involved joints was 3.3. Even the patients with moderate disease had arthropathy. Sixty-four percent of the patients had pain and motion restrictions of the involved joints. Four patients developed intramuscular hematoma. We had patients at several radiological stages of severity. Radiological scores best correlated with age and the total number of involved joints. Various degrees of functional loss, namely disability, were observed. The disability score significantly correlated with the radiological score and age. The results of this study suggest that hemophilic arthropathy is an important problem and that multidisciplinary management is needed. Musculoskeletal care as well as appropriate and timely rehabilitation programs could prevent the development of sequelae.

Key words: hemophilic arthropathy, activities of daily living, rehabilitation, prevention.

The hemophilias are genetically transmitted disorders that are characterized by a quantitative and qualitative deficiency of circulating blood clotting factors. Hemophilia A is caused by a functional deficiency of factor VIII, or antihemophilic factor, and is the most common type, comprising approximately 85 percent of the total number of cases. Hemophilia A is a sex-linked recessive genetic disease affecting men, with women as carriers, although 25 to 30 percent of the cases may be due to new mutations. The severity of the disorder varies from patient to patient. Patients with hemophilia are classified as mild, moderate, or severe depending on the level of circulating coagulant factor. In the mild form, the patient has a functional plasma level of 26 to 60 percent of factor VIII and may bleed excessively only during surgery. In the moderate form, the plasma level is between six and 25 percent, and bleeding may occur during surgery or after trauma. Patients with moderately severe disease have plasma levels of factor VIII between one and five percent those with severe disease have levels below one percent. Patients with moderately severe to severe disease are at a greater risk for bleeding into joints, muscles, and vital organs with minimal or recognized trauma. Spontaneous bleeding into joints is limited to persons with severe hemophilia[1-4]. There appears to be a predilection for large joints, namely the ankles, knees, hips, elbows, and shoulders. The bleeding manifestation requiring treatment most often is acute hemarthrosis (extravasation of blood into joints) and, when frequent, these painful acute episodes may lead to a self-perpetuating synovitis and ultimately to a chronic, deforming arthropathy and disability[5,6].

In this study, our aim was to document the musculoskeletal problems and the disability of 25 hemophiliacs followed-up at the Pediatrics and Physical Medicine and Rehabilitation Departments, Ankara University Faculty of Medicine.

Material and Methods

Twenty-five patients with hemophilia were included in the study. Disease history, age, age at the onset of symptoms, coagulant factor levels, and the average number of yearly bleeding episodes were recorded for each patient. An extensive musculoskeletal evaluation of all joints and soft tissues was performed in all patients. Pain, tenderness, swelling, effusion, synovitis, crepitation, range of motion (ROM) limitation and contractures were assessed as a part of the follow-up protocol. The total number of affected joints in each patient was recorded.

Standard anteroposterior and lateral radiographs of the affected joints were taken for the roentgenographic classification of hemophilic arthropathy. All films were scored on a five point scale (Table I)[7]. This scale was derived from those of Arnold and Hilgartner[3] and Pettersson et al.[8] to provide a simple and reproducible measurement which particularly distinguished those appearances (including joint space narrowing and erosions) signifying irreversible damage to cartilage and bone. If there was a discrepancy, a consensus was reached after a revision of the radiograph by the authors. The scores of all joints were added to give a composite score for each patient.

Table I. Classification of Radiological Changes[7]

0 = Normal
1 = Soft tissue swelling, increased synovial density, juxta-articular osteoporosis
2 = Marginal erosions, bone cysts and joint space narrowing in non-weight bearing joints
3 = Severe joint space narrowing, erosions and cysts, osteophytes, growth anomalies and configurational abnormalities in weight bearing and non-weight bearing joints
4 = Disrupted joint, transarticular bony trabeculae

In addition, we measured the functional status of our patients, because the musculoskeletal impairments caused by hemophilic arthropathy might lead to disability. For this purpose, we used the Juvenile Arthritis Functional Assessment Report for Children (JAFAR-C)[9].

This functional assessment tool was primarily developed for patients with juvenile chronic arthritis and as designed has 23 items about the activities of daily living. From this tool, we chose the most suitable 16 items which could reflect the difficulties that hemophiliac[5] could face in their daily life. We also considered the fact that in using such scales the questions should be convenient and adaptable culturally. The revised assessment tool is shown Table II. The response to the each activity was scored on a scale of 0-2: a score of 0 was given if the action could be accomplished alone without any difficulty all the time over the past week, 1 if it could be done sometimes and 2 if it was almost never done by the patient alone. The total score was calculated as the sum of the scores of all items, assuming a range between 0 and 32.

Table II. Questions Chosen from JAFAR-C[9]

Can you
1. Pull on sweater over head
2. Turn on water faucet
3. Climb into bathtub
4. Wash face
5. Tie shoelaces
6. Pull on socks
7. Brush teeth
8. Stand up from chair without using hands
9. Get into bed
10. Use knife and fork
11. Walk 50 m without help
12. Walk up five steps
13. Reach above head
14. Pick up something from floor from standing position
15. Push open door after turning knob
16. Squat

* Responses are scored 0 for all the time, 1 for sometimes, and 2 for almost never.

JAFAR-C: Juvenile Arthritis Functional Assessment Report for Children.

Descriptive statistics and Spearman's correlation analysis were performed and the statistical significance was set at $p<0.05$.

Results

Demographics and other characteristics of our patients are provided in Table III. The mean age was 17.4 years and the average number of yearly bleeding episodes was 11. The mean coagulant factor level was 4.2 percent (range, 0 to 18). There was a weak association between the factor level and the average number of yearly bleeding episodes ($p>0.05$, $r=-0.22$). The mean number

of involved joints was 3.3 (range, 1 to 7). A total of 82 joints in the study group were found to have hemarthrotic attacks, and the knees (37/82, 45.1%) were the most commonly affected joints followed by elbows (18/82, 22%), ankles (17/82, 20.7%), hips (5/82, 6.1%), and the shoulders (4/82, 4.9%). One patient had involvement of the third proximal interphalangeal joint. Knee and ankle involvement was bilateral in 13 and seven patients, respectively. Moreover, four patients developed intramuscular hematoma (psoas, quadriceps, deltoid and forearm). The patient with psoas hematoma also developed entrapment of the femoral nerve causing severe axonal degeneration of the nerve shown by electroneuromyography. One patient had septic arthritis of the knee. Sixteen patients in this study group had pain and ROM limitations and contractures of the affected joints. Again, knees and elbows were the most commonly restricted joints.

Table III. Demographics and Other Characteristics of the Patients (n=25)

Variables	Min-Max	Mean	SD
Age (years)	4-46	17.4	9.9
Age at onset (months)	0.132	24.4.	34.6
Factor level (%)	0-18	4.2	4.5
# Yearly bleeding episodes	2-72	11	14.4
# Joints involved	1-7	3.3	2
Radiological score	1-16	6.8	4.7
Disability score	0-22	7.5	6.3

The mean radiological score was 6.8 (range, 1 to 16). There was a statistically significant correlation between the radiological score and age ($p<0.05$, $r=0.45$) and the total number of affected joints ($p<0.001$, $r=0.77$). Although it did not reach a significant level, there was an association between the radiological score and the average number of yearly bleeding episodes ($p>0.05$, $r=0.32$).

The patients of this study had various degrees of functional difficulties; the mean disability score was 7.5 (range, 0 to 22). Of the 16 functional activities, squatting, walking up five steps and picking up something from the floor from a standing position were the most difficult activities. The disability score correlated significantly with the radiological score ($p<0.01$, $r=0.69$) and age ($p<0.05$, $r=0.42$). There was a weak correlation between the disability score and total number of involved joints ($p>0.05$, $r=0.33$).

Discussion

Musculoskeletal complications of hemophilia include acute hemarthrosis, subacute or chronic arthritis and hemophilic arthropathy. Patients with hemophilia may also experience soft tissue and intramuscular hemorrhage and, rarely, pseudotumors, septic arthritis and nerve compressions[10]. Hemophilic arthropathy, the total destruction of the joint, develops due to the recurrent hemarthrosis and the specific changes occurring in the synovium and cartilage[4,11,12]. The pathophysiology of this blood-induced joint damage is not known in detail but it is thought to be multifactorial in origin and to include degenerative cartilage mediated and inflammatory synovium-mediated damage. A possible suggested sequence of events may be that intra-articular bleeding initially provokes a non-specific inflammatory response, macrophages accumulate around synovial iron deposits, release monokines, and stimulate production of latent collagenases and prostanoids. The continued leak of red blood cells from the hypertrophied, vascular synovium then produces a vicious cycle of synovitis-bleeding-synovitis[4]. The increased iron load results in further synoviocyte hyperplasia and macrophage accmulation. Degradation of the cartilage matrix through several cartilage-damaging mediators such as enzymes, cytokines, and oxygen metabolites might also start as a direct response to blood[4,11,12]. The clinical findings resemble both degenerative joint diseases and advanced rheumatoid arthritis. The involved joint is enlarged owing to osteophytic bony overgrowth, the range of motion is restricted and subluxation and instability are common. The hemophilic arthropathy is considered to be the most important cause of morbidity in patients with severe hemophilia[6,13]. In the present study, we tried to demonstrate the caharacteristics of joint involvement in hemophiliacs as well as the disability associated with it.

All patients in this study had hemarthrotic attacks; the mean number of affected joints was 3.3, and the most involved joints were the larger joints such as knees, elbows, and ankles, confirming the previous studies[6,7]. Seventy-eight percent of our patients had a plasma coagulant factor level below five percent, and the others were moderately ill. Even the patients with moderate disease had hemarthrotic attacks and various degrees of radiological findings, suggesting that mild or infrequent bleeding

might also start joint damage. Similar results were reported by Steven et al.[7] In fact, it is possible that these patients with moderate illness may not have been admitted to the hospital because of rather silent or less severe clinical presentation. Therefore, examination of all joints should be carried out, even in the absence of a history of hemarthrosis, to identify early cases of arthritis.

There was not a strong correlation between the total number of involved joints and the coagulant factor level. This could be due to the development of a frequently bleeding "target joint" in most patients[14]. Sixty-four percent of the patients had motion restrictions of the involved joints and this had a considerable impact on performing daily activities.

In hemophilic arthropathy, the earliest radiographic findings are seen at the soft tissue; the joint capsule is distended and the intraarticular bleeding demonstrates an increased density. With the progression of the proliferative synovitis, irreversible radiological changes occur. These are periarticular soft tissue thickening and demineralization, marginal erosions, subchondral irregularity and cyst formation, decreased joint space, osteophytes and chondrocalcinosis. The specific radiological features of hemophilic arthropathy are the widening of the femoral intercondylar notch, squaring of the distal patellar margin, enlargement of the proximal radius and flattening of the talus with or without ankle joint ankylosis[10]. Our patients were at several radiological stages. Radiological scores best correlated with age and the total number of affected joints, which we think could be primarily based on the disease duration and resultant increased recurrent hemarthrotic attacks. Moreover, although it was not statistically significant, an association existed between the radiological score and the average number of yearly bleeding episodes.

Despite advances in modern treatment having dramatically reduced the mortality associated with the bleeding episodes of hemophilia, it is not clear whether there has been any impact on the morbidity resulting from hemarthrosis and arthropathy. There have been few studies about the functional loss in hemophiliacs, although it seems to be the most important issue in these people's lives. Ahlberg[15] reported that over half of his group of 102 patients with severe hemophilia had marked-to-severe disabilities as a result of hemophilic arthropathy, eight had to use a wheelchair, and 20 percent required crutches, sticks or other orthopedic appliances. He also described a relation of disability to age. Recently, Iwata and his colleagues[16] studied the limitation of joint function in 97 helophiliacs in relation to functional limitations and/or activities of daily living. Their analysis showed that full flexion of the lower limbs was easily limited in these patients and that this deterioration was difficult to prevent, resulting in marked disability. They also concluded that the functional limitation level differed significantly by age group. Heijnen et al.[17] worked on the estimation of severity of joint movement limitation giving rise to disabilities. They found that many patients started to compensate with another joint motion if one joint in the chain of a limb was limited. They also emphasized that functional jüoint motion may differ between cultures and countries; slight restrictions in lower limbs are disabling in Asian countries where people squat and use an Eastern type of toilet, whereas in Western countries knee flexion of 100° might enable the patient to climb stairs and ride a bicycle. Mild-to-moderate disabilites were observed in the present study and the most difficulty activities for our patients were squatting, walking anda picking up something from the floor from a standing position. Disability correlated strongly with age and radiological score, indicating that severe arthropathy increased the functional loss. Multiple joint involvement increased the disability, and this condition was suggestive of the difficulty in compensation which has also been reported before[17].

Overall, our study and the others show that hemophilic arthropathy is an important problem, and that multidisciplinary management of this condition might provide good results. Although costly from an economic point of view, prophylaxis has effectively prevented joint and musculoskeletal disease in severe hemophilia[18-20].

Additionally, patient and family education, proper and efficient rehabilitation programs and the maintenance of physical activity are important preventive measures[13,21]. We believe that rehabilitation and musculoskeletal care could prevent the appearance of sequelae and improve the quality of life for hemophiliacs.

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