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Original Article

Muscle strength and joint health in children with hemophilia: a cross-sectional study

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ABSTRACT

Background and objectives. We aimed to evaluate joint health in children with hemophilia (CwH) and to investigate the effects of hemarthrosis on the musculoskeletal system.

Method. Forty-one CwH aged between 6-18 years participated in the study. Joint health status was evaluated according to Hemophilia Joint Health Score (HJHS). Pain intensity level was assessed in resting and in activity using Visual Analog Scale. Range of motion was measured with goniometer and muscle strength was assessed with digital dynamometer. Arthropathic joints were examined in three groups named knee, elbow and ankle.

Results. Physical examination revealed arthropathy findings to be found in 29 knee, 19 elbow and 18 ankle joints. The median of flexion angle of the affected side were 120°, 122° and 12° for the knee, elbow and ankle and extension losses of these joints were 5°, 7° and 0, respectively. In CwH having knee and elbow arthropathy, index joint HJHS was found to be significantly higher than those with ankle arthropathy ($p < 0.01$). The flexor and extensor muscle strength significantly decreased in 11 CwH with unilateral elbow arthropathy compared to the non-arthropatic side ($p < 0.05$). In 15 CwH with unilateral ankle arthropathy decreased in the extensor muscle strength (plantarflexors) ($p < 0.05$). Extension loss showed a good correlation with index HJHS of elbow, knee and ankle joints, respectively. ($r_s = 0.599, 0.576, 0.606$, $p < 0.01$). We observed that the muscle strength of elbow flexors/extensors and ankle extensors were significantly decreased compared to the non-arthropathic side. However this situation was not detected in knee joint despite having highest index HJHS.

Conclusion. Our findings indicate that hemarthrosis may cause more muscle strength loss in the upper extremity than the lower extremity. Furthermore, extension loss was found to be an important parameter in physical examination of hemophilic arthropathy. Musculoskeletal system should be evaluated comprehensively at regular intervals and when necessary rehabilitative treatment should be planned.

Key words: hemophilia, arthropathy, muscle strength, range of motion, physical examination.

Hemophilia is a rare hereditary bleeding disorder that occurs in partial or complete deficiency of clotting factor VIII (in hemophilia A) and factor IX (in Hemohilia B).[1,2] Severity and frequency of bleedings are closely related to the factor levels.[3] Severe hemophilia is defined as factor basal level less than 1%, moderate hemophilia between 1-5% and mild hemophilia more than 5%.[1,4] Severe hemophilia is characterized by spontaneous musculoskeletal bleedings that occur mostly in the joints and is called hemarthrosis.[5] Recurrent hemarthrosis leads to a vicious cycle in the joint which leads to synovial hypertrophy and damage to the cartilage, followed by hemophilic arthropathy of the joint. It causes irreversible joint destruction due to the progression of deformation in the joint.[6]

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Nowadays, the primary aim of hemophilia treatment is the prevention of hemophilic arthropathy.[7] Despite new developments in drug therapies and advances in gene therapy which have resulted in increased life-expectancy and quality of life for hemophilic individuals, uncertainties about how to rehabilitate existing joint damage of individuals with musculoskeletal problems and difficulties in accessing expert physiotherapists in hemophilia are currently the biggest challenges.[7,8] In terms of International Classification of Functioning (ICF), Disability and Health developed by WHO, it is known that muscle weakness and joint limitation in hemophilia negatively affects activity and participation, therefore, it is important to evaluate muscle strength and joint health conditions in children with hemophilia (CwH).

Hemophilia Joint Health Score (HJHS) is routinely used in assessing the prognosis of the disease and the effectiveness of the treatment. HJHS was designed to monitor the disturbances in mild or non-mild joints in CwH who received prophylactic treatment between 4-18 years of age.[9] HJHS was more sensitive than X-ray and safe in detecting early changes in joints.[9,10] The assessment of joint health in CwH should be routinely performed every six months with physical examination and every once a year with radiological assessment.[11,12]

In previous studies in hemophilia, the total score of HJHS was used in the evaluation of musculoskeletal disorders. However, the relationship between the dynamometric measurement of muscle strength and the index joint scores of HJHS was examined separately in our study. The aim of this study was to evaluate joint health in CwH and to investigate the effects of hemarthrosis on musculoskeletal system.

Material and Methods

This study was an observational cross-sectional study including 41 CwH aged between 6-18 years old and was conducted between February and April 2018 at Yuzuncu Yil University Department of Pediatric Hematology. The exclusion criteria of the study was the history of bleeding in any joint in the last two weeks, having any disease related to connective tissue, having a neurological disease or cognitive impairment and having undergone surgery related to joints. CwH who had participated in no regular physical activity and sports were included in the study.

In order to carry out the study, the approval of the required ethics committee was obtained with the numbered 03/31.01.2018 of the Ethics Committee of the Yuzuncu Yil University. Verbal consent was obtained from participants and written consent was obtained from the parents of all children.

Assessments

Hemophilia Joint Health Score (HJHS)

HJHS is a haemophilia-specific assessment method that assesses disorders occurring in six key index joints in its current version. The index joints are hinged joints such as knee, elbow and ankle joint with an excessive synovial fluid content and they are exposed to more mechanical stresses.[13] Swelling, duration of swelling, muscle atrophy, crepitus during motion, flexion loss, extension loss, joint pain and muscle strength were evaluated in eight sub-headings parameters.[8,9]

Range of motion (ROM) (flexion and extension loss) and muscle strength may reflect situation of joint function and structure. Others such as crepitation, swelling, duration of swelling may involve changes in the joint which do not correlate with disability.[11] The maximum damage score for each index joint is 20 points per joint. The last subtitle of the HJHS was the global gait score and its maximum score was 4 points. The maximum total HJHS score is 124 points.[8,9] High scores indicate poor joint health. The HJHS score of the index joints and total HJHS score of the participants were recorded.

Physical Examination

Physical examination which is a practical and inexpensive assessment method of joint, is often used to measure structural and functional joint damage.[8] Physical examination was performed by the same physiotherapist who was non-blind to the study, because this is a very new area of specialization for physiotherapists and there were no other experienced physiotherapists to evaluate CwH in our department. Evaluation of the joint ROM were performed using the same standardized goniometric measurements. The flexion angles and extension loss of the knee and elbow joints, the dorsiflexion and plantarflexion angles of the ankle joints were measured for all patients.[14] Pain intensity levels were evaluated both on rest and activity by using visual analogue scale (VAS). This consists of a 10 centimeter straight line which should be marked by the patients according to the pain intensity level. A level of ten centimeters shows severe pain intensity while zero centimeters indicate no pain on the line.[15]

The evaluation of muscle strength was performed using a digital dynomometer. The strength of the extensor and flexors muscles of the knee joint were measured during sitting position with hip and knee in 90° flexed position by applying resistance over the malleolus.[16,17] The strength of the extensor and flexor muscles of the elbow joint was measured while the elbow joint was flexed at 90° by applying the forearm resistance in the sitting position. To measure the strength of the dorsiflexors and plantar flexors of the ankle the joint lower legs of the patient were stabilized in the supine position and resistance was given from the metatarsal head.[17] The average muscle strength was recorded with the digital dynamometer as pound (1 pound = 0.4535kg).

Arthropathic joints were examined in three groups named as knee, elbow and ankle.

Statistical Analysis

Statistical analysis were performed using the SPSS software version 22. The variables were investigated using visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirrov / Shapiro-Wilk tests) to determine whether or not they were normally distrubuted. Descriptive analysis were presented using means and standard deviation for normally distrubuted variables and median and minimum-maximum values (Physical charesteristics of participants). In the event the data did not show normal distribution between the groups, median values and minimum-maximum values were expressed and the non-parametric Kruskal-Wallis test was used. The correlation coefficients and their significance were calculated using the Spearmen test. In the cases of unilateral arthropathy in the groups, the dependent variables were presented using means and standard deviations for normally distrubuted variables and were compared with the Student t-test while not normally distrubted variables were compared with the Mann Whitney U test. A p-value of less than 0.05 was considered to show a statistically significant result.

Results

Of the 41 CwH, 39 had hemophilia A, 2 had hemophilia B and the the phenotype of 37 (90%) were severe and of 4 (10%) were mild. Three patients (7%) had inhibitor. The mean age (12.8 ± 3.7), height (146.2 ± 22.8) and body weight (43.0 ± 19.4) of the 41 CwH who participated in the study. Of these patients 21 CwH having arthropathy showed more than one index joint. Arthropathy was not found in the index joints of 6 participants.

The index joints HJHS, total HJHS, resting and activity pain levels of the participants are presented in Table I.

Physical examination revealed arthropathy in 29 knees, 19 elbows and 18 ankle joints groups and these joints were examined in all three groups.

There was no statistically significant difference between the ages (p=0.429), height (p=0.270) and

Table I. HJHS and VAS scores of all participants.

Parameters	Median (Min-max)
HJHS-Right Elbow	0 points (0-9 points)
HJHS-Left Elbow	0 points (0-7 points)
HJHS-Right Knee	2 points (0-13 points)
HJHS-Left Knee	2 points (0-11 points)
HJHS-Right Ankle	1 points (0-7 points)
HJHS-Left Ankle	0 points (0-3 points)
Total HJHS	9 points (2-32 points)
Activity VAS	3 cm (0-8 cm)
Resting VAS	0 cm (0-9 cm)

HJHS: hemophilia joint health score, VAS: visual analog scale.

body weights (p= 0.134) when the CwH were divided into classes according to arthropathic joints. Activity VAS (p= 0.446) and resting VAS (p= 0.760) were used to assess pain intensity level and no statistically significant difference was found between the groups. In CwH with knee and elbow arthropathy, index joint HJHS was found to be significantly higher than those with ankle arthropathy (p= 0.002). HJHS scores and physical assessment results (median values, minimum-maximum) according to the joints are given in Table II. Our study found that arthropathy developed in joints as a result of recurrent bleeding episodes showed a decrease in flexion angle and an increase in extension loss. Physical examination of groups showed in Table III.

Table IV showed the comparision of muscle strength in unilateral arthropathy. In 11 CwH with unilateral elbow arthropathy flexor (p= 0.041) and extensor (p= 0.021) muscle strength was significantly reduced compared to non-arthropathic side. In 19 CwH with unilateral knee arthropathy the extensor (p= 0.182) muscle group and the flexor (p= 0.385) muscle strength decreased in the affected joint but was statistically not significant. In 15 CwH with unilateral ankle arthropathy, the decrease in the dorsiflexor muscle strength (p= 0.191), which functions as the flexion of the joint, was not statistically significant while the decrease in the plantar flexor muscle strength acting as extension was significant (p= 0.040).

Extension loss was moderately correlated with elbow, knee and ankle HJHS (respectively r_s=0.599, 0.576, 0.606, p <0.01) and is displayed in Fig. 1. Flexion angle showed a negative moderate correlation with flexor muscle strength (r_s=0.523, p <0.05) and was strongly

Table II. Physical characteristics, HJHS and VAS scores of participants according to arthropatic joints.

	Knee (n= 29)	Elbow (n= 19)	Ankle (n= 18)	p value
Age (years)	14 (7-18)	16 (9-18)	12 (7-18)	0.429
Height (cm)	150 (107-180)	170 (121-176)	139 (107-179)	0.270
Weight (kg)	39 (17-76)	60 (21-75)	32 (17-71)	0.134
Resting VAS (cm)	0 (0-9)	0 (0-5)	0 (0-9)	0.760
Activity VAS (cm)	4 (0-7)	5 (0-8)	4 (0-7)	0.446
HJHS (Index joints)	5 (2-13)	5 (1-9)	3 (1-7)	0.002*

*Kruskall-Wallis test, p<0.05, Median (Minimum-Maximum) Values
HJHS: Hemophilia joint health score, VAS: visual analog scale.

Table III. Physical examination of groups.

	Knee (n= 29)	Elbow (n= 19)	Ankle (n= 18)
Flexion angle (°)	122 (90-135)	120 (90-145)	12 (7-20)
Loss of extension (°)	5 (0-10)	7 (0-35)	0 (0-14)
Flexor muscle strength (lbs)	17.7 (7.3-27.5)	16.8 (8.8-30.1)	13.4 (5.1-18.4)
Extansor muscle strength (lbs)	16.6 (8.1-32.2)	12.1 (7.8-17.3)	14.0 (7.7-24.5)

Median (Minimum-Maximum) Values

Table IV. Comparision of muscle strength in unilateral arthropathy.

Joints	Muscle Strength	Affected Side (pound)	Non-Affected Side (pound)	t/z	p
		Mean±SD	Mean±SD		
Knee joint	Flexors	16.9 ± 6.5	18.7 ± 6.3	t=-0.880	0.385
(n=19)	Extensors	18.9 ± 6.2	21.8 ± 6.9	t=-1,362	0.182
Elbow joint	Flexors	17.5 ± 3.8	21.2 ± 4.1	t=-2.189	0.041*
(n=11)	Extensors	11.6 ± 2.5	14.4 ± 4.8	t=-2.499	0.021*
Ankle joint	Dorsiflexors	13.4 ± 3.3	16.4 ± 5.2	z=-1.307	0.191
(n=15)	Plantarflexors	15.6 ± 4.5	18.7 ± 4.2	z=-2.054	0.040*

* Student's t-test was used knee and elbow joint, Mann-Whitney U test was used in ankle joint p<0.05

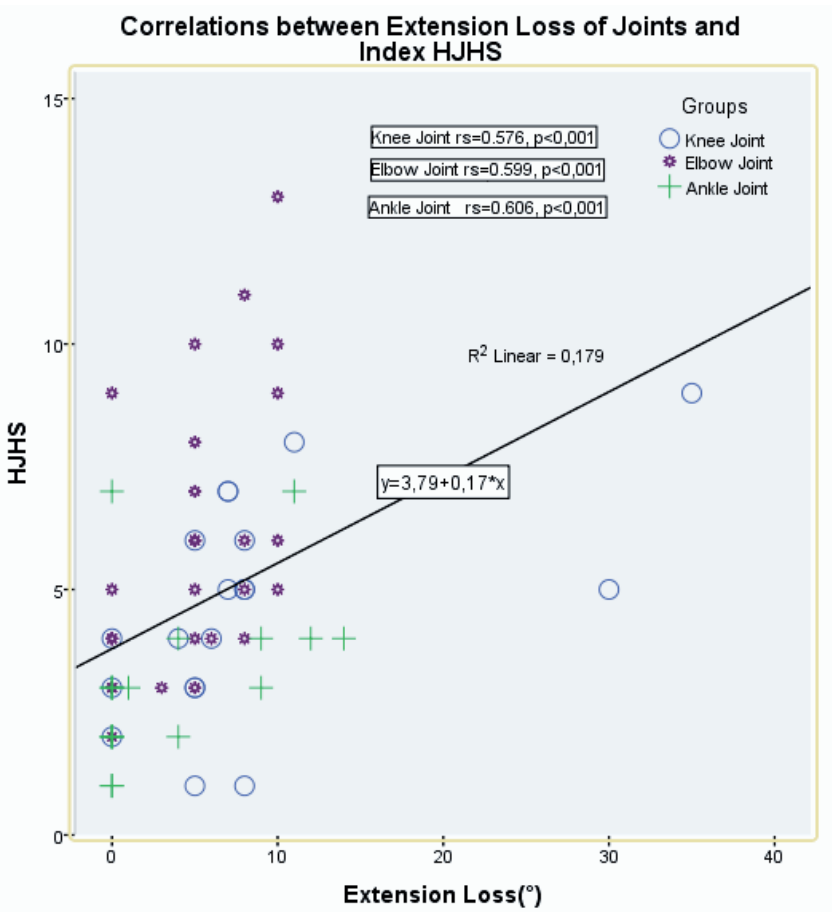

Fig. 1. Correlations between extension loss of joints and index HJHS.
HJHS: Hemophilia Joint Health Score

correlated with extensor muscle strength (r_s= 0.711, p <0.01) in elbow arthropathy. HJHS showed a negative moderate correlation with flexion angle (r_s= 0.621, p <0.001) and extensor muscle strength (r_s= 0.517, p <0.01), a negative weak correlation with pain on rest (r_s= 0.410, p <0.05) in knee arthropathy. In ankle arthropathy dorsiflexion angle showed a negative moderate correlation with pain on rest (r_s= 0.637, p <0.005) and pain on activity (r_s= 0.677, p <0.005).

Discussion

Recurrent joint bleedings are the hallmark of hemophilia that leads to progressive changes in the musculoskeletal system over the years. Our study supports the finding that hemarthrosis leads to decreased joint mobility and muscle strength in CwH. Joint health status can be improved by correct treatments in the long-term after frequent evaluations.

In the literature hemophilia A is more prevalent than hemophilia B and approximately 85% of patients have been reported to be hemophilia A.[2] The distrubution of hemophilic patients in our study was in accordance with the results of the literature. Inhibitory development in our study was 7%, Turkey Inhibitor Screening Project which was completed in 2010 found 13% inhibitor development rate in severe hemophilia patients. In our study inhibor results are consistent with the literature.

In this study we observed that the most common arthropathic joints in CwH were knee, elbow joint and ankle joint, respectively. Hemophilic arthropathy was commonly seen in knee joint due to lack of internal bone stability, three-dimensional movements, load bearing function and possible reasons such as exposure to trauma.[5] Stephensen et al.[13] showed that knee joint was the most common bleeding joint in individuals who cannot access prophylactic treatment routinely.[7] In the adolescent period, elbow joint has been damaged more because of a wider range of motion in daily living activities and frequent use. Deschamps et al.[18] showed that the ankle joint was mostly affected due to easy access to prophylactic treatment. In our country prophylaxis treatment has been widespread since 2010. In this study, ankle arthropathy was more common in the younger age groups, whereas knee and elbow joint arthropathy increased with age.

Soucie et al.[19] showed that healthy male individuals aged between 9-19 years normative values of knee flexion, elbow flexion and ankle dorsiflexion were 142°, 148° and 16°, respectively. In our study, median values of arthropathy joints were 122°,120° and 12°, respectively. Cuesta-Barriuso et al.[15] found that dorsiflexion and plantarflexion angles were 7 degrees and 37 degrees in patients with hemophilic arthropathy of the ankle aged between 20-44 years and those angles were far below the normative values. Goto et al.[17] found that arthropathy in knee and elbow joints as the severity of the disease progress, ROM in both flexion and extension showed significant decreases. As haemophilic arthropathy severity progresses osteophytis and osteochondral cysts form so that joint surface becomes irregular and consequently lead to narrowing of the joint space. These changes may resulted with decreases in joint ROM.

The index joint HJHS was significantly higher in hemophilic individuals having knee and elbow arthropathy than in those having ankle arthropathy ($p < 0.01$). In a study Tusell et al.[20] assessed patients with clinical examination and radiological evaluation and they revealed that the most effected joint and highest score was found in knee by clinical examination and in ankle joint by radiological score.[20] The reason why ankle arthropathy is low in HJHS may result from the low proportional loss of the ankle ROM relatively to those of the knee and elbow joints. Hence, the highest radiographic score of ankle arthropathy has been considered that it is not less severe than knee and elbow arthropathy.

In the current study when the unilateral arthropathy of the knee, elbow or ankle joints were compared with the non-arthropathic side, it was seen that the muscle strength of the elbow joint on the arthropathic side was significantly less than the non-arthropathic side. These results were found in accordance with the literature. Falk et al.[21] evaluated muscle strength of hemophilic children using an isokinetic device and reported that elbow flexor and extensor muscle strength significantly decreased in the hemophilia group. We thought that muscle strength may vary depending on the use of the elbow joint in activities. CwH

with elbow arthropathy mostly protects elbow joints and they don't use involved elbow joint movement frequently. They can compensate the elbow movements with the uninvolved elbow joint during activities. Therefore, decreases in muscle strength in studies may be related with inactivity or disuse of the joint movement due to fear of pain and re-bleeding.

The knee flexor and extensor muscle strength decreased in the arthropatic side but decreased in flexors and extensors muscle strength was statistically not significant in our study. As the knee joint is used continously in gait patern, it is expected that significant loss of muscle strength cannot occur. Similar results were found in the study conducted by Goto et al. and they found the relationship between joint function and severity of arthropathy.[17] Lobet et al.[22] showed in their study of isokinetic measurement of ankle joint arthropathy, that CwH have no significant difference in muscle strength compared to their healthy peers. In our study, the decrease in dorsiflexor muscle strength was not significant, but the decrease in plantar flexors muscle strength was significant. This observation may be due to the very simple change in load distribution during the gait cycle especially the heel off phase. Lower extremity muscle strength is very important in many daily life activities and reflects the functional capacity of the hemophilics. Weakness of the knee extensors is known to be characteristic of adult severe hemophilia, and in our study there was no significant difference in the CwH compared to the side without arthropathy. Knee muscles is used continuously in daily life activities such as standing, walking, squatting and the joints are always exposed to some loads. Thus, the muscles of knees cannot be inactive and having more stimulus in daily activities.

One of the limitation of this study was that radiological imaging could not be performed to evaluate joint health of CwH. If radiological imaging methods could have been used in the study, more detailed data could have been obtained for hemophilic arthropathy. The other limitation of this study was that we could not to assess functional independence and quality of life of the patients although both of them are very important musculoskeletal outcome tools. Turkish validation-reliability of these tests have not been completed yet, therefore we could not use them.

In summary, we observed that muscle strength was significantly decreased in CwH especially elbow flexors/extansors and ankle extansors compared to the non-arthropathic side but not in knee muscles despite having the highest index HJHS scores. Our findings revealed that hemarthrosis cause more muscle strength loss in the upper extremity than the lower extremity. Therefore, both upper extremity and lower extremity muscles should be strengthened from early ages in hemophilia. Furthermore extension loss was found to be another important parameter in physical examination of arthropathy and may be the cause of a decrease in the muscle strength in the hemophilic arthropathy. The musculoskeletal system should be evaluated comprehensively at regular intervals and when necessary, rehabilitative treatment should be planned.

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