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BRIEF REPORT

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Survey of motor function and activities of daily living in hemophilia patients with HIV

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Abstract: This study aimed to clarify the current status of motor function, activities of daily living (ADL), and instrumental ADL (IADL) in hemophilia patients with HIV infection due to treatment with non-heat-treated blood products as they now enter middle and old age. Participants were 70 such patients (mean age, 52.1 years), and their range of motion (ROM), muscle strength, extremity circumference, walking speed, ADL, and IADL were evaluated at checkups of motor function, ADL, and IADL that were held during patients' association meetings. Results showed that ROM was limited in all joints. Ankle dorsiflexion, hip abduction, and shoulder abduction were particularly restricted. Decreased muscle strength was most frequent in ankle plantarflexion, followed by hip extension. The proportion of patients with walking speed and grip strength below reference values increased with age. Walking speed was 73.9-110.9% of reference values. Factors affecting walking speed were knee flexion, ankle dorsiflexion, and hip extension muscle strength. Grip strength was 58.0-83.5% of reference values. Thigh girth most greatly differed between the patients and healthy individuals. Among the ADL items, "standing up from the floor" was reported as "difficult"/"cannot do" by 45.7% of the patients. The most common IADL problem was "putting away futons", which 17.2% responded was "difficult"/"cannot do". Parents were the most common helpers with household tasks (12.9%). "Decreased muscle strength/limited ROM" was the most frequently reported troublesome problem (35.7%). These results reveal the current status of motor function, ADL, and IADL limitations in hemophilia patients with HIV.

***Keywords*:** hemophilia patients with HIV, aging, ADL, IADL, motor function, multicenter study

Introduction

In Japan mostly between 1982 and 1985, about 2,000 hemophilia patients, or about 40% of these patients, were infected with human immunodeficiency virus (HIV) due to treatment with non-heat-treated blood products (*1*). Since the 1980s, advances in blood coagulation factor products and home self-injection therapy have dramatically improved the prognosis and quality of life (QOL) of hemophilia patients, and the average age of death has become almost the same as that of the general male population (*2-4*). With longer life expectancy, hemophilia patients are now entering middle to old age for the first time. At the same time, advances in the treatment of HIV infection have dramatically improved its prognosis and life expectancy (*5*). On average, hemophilia patients with HIV infection caused by non-heat-treated blood coagulation factor products are entering their fifties (*6*).

Although some previous studies have investigated motor dysfunction and ADL in hemophilia patients entering middle and old age, there have been no multicenter studies. Moreover, no report has specifically focused on patients affected by adverse events due to

blood products. Therefore, for the first time in Japan, in this study we investigated the current status of motor function, activities of daily living (ADL), and instrumental ADL (IADL) in hemophilia patients with HIV infection due to contaminated blood products as they enter middle and old age, by performing checkups of motor function, ADL, and IADL during patients' association meetings that were held in Hokkaido, Sendai, Tokyo, Nagoya and Beppu between August and December 2019.

Patients and Methods

Participants in this multicenter study were 70 hemophilia patients with HIV infection due to contaminated blood products who were members of a patients' association and who provided written informed consent.

Basic attributes

Sex and age of the patients were examined.

Joint range of motion (ROM)

Bilateral passive shoulder flexion/abduction, elbow flexion/extension, forearm pronation/supination, hip flexion/abduction/extension, knee flexion/extension, and ankle dorsiflexion/plantarflexion were evaluated.

Muscle strength

The manual muscle test (MMT) was evaluated for bilateral passive shoulder flexion/abduction, elbow flexion/extension, forearm pronation/supination, hip flexion/abduction/extension, knee flexion/extension, and ankle dorsiflexion/plantarflexion, while considering the burden on the joints.

Grip strength

Grip strength was measured twice on each side while the patient was seated with the elbow extended, with an approximately 30-s rest between measurements.

Walking

Patients were instructed to walk quickly for 10 m, which was timed and analyzed.

Girth measurements

The girth of the bilateral upper and lower extremities was measured using a tape measure in a sitting position at the end of an examination table and in the supine position. The maximum girth of the upper arm and forearm in elbow extension and the maximum girth of the lower leg and the thigh at 10 cm proximal from the upper edge of the patella were measured.

ADL

ADL was evaluated in a one-on-one semi-structured interview using questions from an interview guide with the scale developed by Goto *et al.* (*7*).

IADL

IADL was evaluated in a one-on-one interview. Patients were asked about self-injection therapy for hemophilia, in addition to putting away futons, laundry, cooking, moving furniture, cleaning, shopping, and using a phone, with reference to the Frenchay Activities Index developed by Holbrook *et al.* (*8*). The response options for each question were "can do without problems", "difficult", and "cannot do".

Interview survey on the person who mainly performs household tasks

We asked who mainly performs household tasks.

Interview survey on things that are troublesome

Patients were asked to list up to three things that they currently find troublesome.

Analysis

The mean and standard deviation were calculated for joint range of motion. Muscle strength was measured using the MMT, and the proportions of the patients with each score from 1 to 5 were obtained. The individual means of the right and left grip strengths were calculated and the proportion of patients with grip strength below age-group reference values (*9*) was determined. The proportion of patients with walking speed below age-group reference values (*10*) was also determined. To investigate the factors affecting walking speed, we performed multiple regression analysis with walking speed as the objective variable and joint ROM, muscle strength of the lower extremities, and grip strength as explanatory variables. Patients were divided into 10-year age groups, and the mean girth measurements were compared with those of healthy individuals. Ratios relative to standard values were determined for grip strength, walking speed, and girth measurements. The answers for the ADL and IADL items were divided into three groups according to response ("can do without problems", "difficult", and "cannot do") and the proportion of patients in each group was determined for each question. A simple tabulation was performed for the answers to "things that are troublesome" and "the person who mainly performs

household tasks". SPSS version 26 (IBM Corp., Armonk, NY) was used for analysis. The significance level was set at 5%.

Ethical considerations

This study was approved by central review at the Ethics Review Committee of the National Center for Global Health and Medicine (approval number, NCGM-G-003242-00), and appropriate ethics procedures were followed at each participating facility.

Results and Discussion

Basic attributes

Patients were all male, with a mean age of 52.1 (standard deviation, 9.08) years.

Joint ROM

Table 1 shows the results for joint ROM. Patients' mean ROM values were below the reference values for all joints evaluated. Ankle dorsiflexion, hip abduction, and shoulder abduction showed especially restricted ROM.

Muscle strength

Table 2 shows the muscle strength results. Muscle strength was most frequently decreased in ankle plantarflexion, with MMT scores of 3 and 2 in 8.5% and 27.1% of the patients, respectively. Hip extension was the second most frequently decreased, with MMT scores of 3 and 2 each in 5.3% of the patients, followed by hip abduction, with MMT scores of 3 and 2 in 3.0% and 3.7% of the patients, respectively.

Grip strength

Table 3 shows the results for grip strength. Compared with healthy individuals by age group, the proportions of patients with grip strength below the reference values were 75.0% for patients in their 30s and 96.4% for those in their 40s. All patients in their 50s and 60s

Table 1. Range of motion in the study population of 70 hemophilia patients with HIV infection from contaminated blood products

Motion	*n*	Mean (deg)	SD (deg)	Ratio relative to the reference value (%)
Shoulder flexion	138	147.2	20.6	81.8
Shoulder abduction	138	143.3	30.5	79.6
Elbow flexion	138	125.6	19.6	86.6
Elbow extension	138	−22.4	22.3	87.2
Elbow pronation	138	73.2	18.2	81.3
Elbow supination	138	79.4	24.9	88.2
Hip flexion	138	105.8	18.2	84.6
Hip extension	138	14.4	13.5	96.0
Hip abduction	138	32.6	13.4	72.5
Knee flexion	138	116.1	31.5	89.3
Knee extension	138	−8.5	13.3	95.3
Ankle dorsiflexion	138	2.1	11.0	10.4
Ankle plantarflexion	138	35.1	11.6	78.0

Values are the percentage of the target joints. Ratio relative to the reference value (%) = [(mean measurement value of the target joint)/(reference ROM of the target joint)] × 100. SD, standard deviation.

Table 2. Muscle strength measurements

Muscle strength (MMT)	*n*	5	4	3	2	1
Motion						
Shoulder flexion	140	90.7%	7.9%	1.4%	0.0%	0.0%
Shoulder abduction	138	88.4%	9.4%	2.2%	0.0%	0.0%
Elbow flexion	138	91.3%	8.0%	0.7%	0.0%	0.0%
Elbow extension	126	85.7%	13.5%	0.8%	0.0%	0.0%
Forearm pronation	138	84.1%	15.9%	0.0%	0.0%	0.0%
Forearm supination	140	82.9%	16.4%	0.7%	0.0%	0.0%
Hip flexion	137	76.6%	21.2%	2.2%	0.0%	0.0%
Hip abduction	134	73.9%	19.4%	3.0%	3.7%	0.0%
Hip extension	133	66.2%	23.3%	5.3%	5.3%	0.0%
Knee extension	133	85.0%	12.8%	2.3%	0.0%	0.0%
Ankle dorsiflexion	135	85.9%	11.9%	2.2%	0.0%	0.0%
Ankle plantarflexion	118	44.1%	20.3%	8.5%	27.1%	0.0%

Values are the percentage of target joints. MMT, manual muscle test.

Table 3. Grip strength and walking speed

Age	Grip strength				Fast walking speed			
	n	Mean (kg)	Ratio relative to the reference value (%)	Patients below the reference value (%)	*n*	Mean (m/min)	Ratio relative to the reference value (%)	Patients below the reference value (%)
30s	4	39.6	83.5	75.0	4	133.1	110.9	25.0
40s	28	30.7	65.6	96.4	27	102.6	85.5	77.8
50s	23	28.3	62.3	100.0	21	89.9	78.2	90.5
60s	14	24.2	58.0	100.0	13	85	73.9	100.0

Grip strength ratio relative to the reference value (%) = [(mean grip strength of all patients)/(reference value)] × 100. Fast walking speed ratio relative to the reference value (%) = [(mean fast walking speed of all patients)/(reference value)] × 100.

Table 4. Girth measurements

Age		Upper arm				Forearm		Thigh				Lower leg			
		Right (cm)	Left (cm)	Ratio relative to the reference value	Upper arm reference value (cm)	Right (cm)	Left (cm)	Right (cm)	Left (cm)	Ratio relative to the reference value	Thigh reference value (cm)	Right (cm)	Left (cm)	Ratio relative to the reference value	Lower leg reference value (cm)
30s	Mean	29.5	28.8	—	—	27.0	25.8	47.8	47.3	—	—	36.5	37.3	—	—
n = 2	SD	0.50	0.25		—	0.50	0.75	2.25	0.25		—	1.50	0.75		—
40s	Mean	25.9	26.5	90.3%	29.0	25.1	24.7	42.4	41.3	84.5%	49.6	33.5	32.8	89.7%	36.9
n = 13	SD	3.59	4.19		2.6	2.10	2.16	8.46	7.25		3.80	4.81	4.75		2.70
50s	Mean	25.8	26.7	90.8%	28.9	23.9	24.4	38.0	39.0	78.7%	48.9	30.8	32.0	84.8%	37.0
n = 9	SD	3.82	4.19		2.4	2.96	2.26	5.27	4.52		3.80	2.69	3.54		2.70
60s	Mean	24.8	24.8	79.4%	28.1	23.6	23.5	38.2	36.3	88.3%	46.9	31.2	30.4	86.6%	35.6
n = 5	SD	4.32	5.27		2.2	1.98	1.84	3.23	4.46		3.50	3.80	4.17		2.60

Upper arm girth was measured in elbow extension. We were unable to obtain a reference value for patients in their 30s. Reference values for patients in their 40s, 50s, and 60s were taken from reference 11. Ratio relative to the reference value (%) = [(mean value of the target site of all patients)/(reference value of the target site)] × 100. Ratios relative to the reference values (%) were obtained for the mean of the left and right sides. SD, standard deviation.

had grip strength below the reference values. Muscle strength relative to the reference values was 83.5%, 65.6%, 62.3%, and 58.0% for patients in their 30s, 40s, 50s, and 60s, respectively.

Walking speed

Table 3 shows the results for walking speed. Walking speeds by age group were below reference values of healthy individuals for 25% of patients in their 30s, 77.8% of those in their 40s, 90.5% of those in their 50s, and all patients in their 60s. Measured values of the patients in their 30s were above the reference value with a ratio relative to the reference value of 110.9%, while the ratios were 85.5%, 78.2%, and 73.9% for patients in their 40s, 50s, and 60s, respectively.

Factors contributing to walking speed were knee flexion ROM (standardized coefficient, 0.446), hip extension ROM (0.418), and ankle dorsiflexion ROM (0.216).

Girth measurements

Table 4 shows the results for the four girth measurements taken. Mean values were highest for patients in their 30s at all measurement sites and tended to decline with age. Compared with reference values of healthy individuals in their 40s and 60s (*11*), the measured values were below the reference values at all sites in all age groups. In particular, the difference was the largest for thigh girth, at 84.5% of the reference value for patients in their 40s, 78.7% in their 50s, and 77.4% in their 60s.

ADL

Table 5 shows the ADL results. The most frequent difficulty in ADL was "standing up from the floor", which 64.3% of the patients reported as "difficult" or "cannot do". The second most common difficulty in ADL was "squatting", which 62.9% reported was "difficult" or "cannot do". This was followed by "climbing up and down stairs", which was either "difficult" or "cannot do" for 54.3% of the patients.

IADL

Table 5 shows the results for IADL. In terms of

Table 5. ADL and IADL

	n	Can do without problem	Difficult	Cannot do	Difficult/cannot do
ADL					
Standing up from the floor	70	35.7%	45.7%	18.6%	64.3%
Squatting	70	28.6%	22.9%	40.0%	62.9%
Climbing up and down stairs	70	41.4%	51.4%	2.9%	54.3%
Sitting on the floor	70	38.6%	24.3%	21.4%	45.7%
Walking on a slope	70	47.1%	40.0%	2.9%	42.9%
Clipping toenails	70	64.3%	28.6%	5.7%	34.3%
Washing face with both hands	70	72.9%	12.9%	12.9%	25.7%
Buttoning and unbuttoning top button	70	74.3%	22.9%	2.9%	25.7%
Washing body	70	74.3%	24.3%	2.9%	25.7%
Putting on and taking off socks	70	74.3%	18.6%	1.4%	25.7%
Walking without a cane	70	75.7%	10.0%	2.9%	21.4%
Sitting on a chair	70	88.6%	10.0%	0.0%	10.0%
IADL					
Putting away futons	70	55.7%	5.7%	22.9%	28.6%
Laundry	70	74.3%	12.9%	8.6%	21.4%
Cooking	70	74.3%	10.0%	11.4%	21.4%
Moving furniture	70	78.6%	5.7%	8.6%	14.3%
Self-injection	70	82.9%	2.9%	11.4%	14.3%
Cleaning	70	88.6%	5.7%	4.3%	10.0%
Shopping	70	90.0%	4.3%	5.7%	10.0%
Using a phone	70	97.1%	1.4%	0.0%	1.4%

Values are the percentage of patients. ADL, activities of daily living; IADL, instrumental activities of daily living.

difficulties in IADL, 5.7% of the patients responded that "putting away futons" was either "difficult" or "cannot do". Next was "laundry", with 12.9% and 8.6% responding "difficult" or "cannot do", and then "cooking" at 10% and 11.4%, respectively.

Persons who mainly perform household tasks

The persons who mainly performed household tasks were the patients themselves (38.6%), followed by their spouses (25.7%), parents (12.9%), both patients and spouse (8.6%), both patients and parents (4.3%), siblings (2.9%), and parents- or siblings-in-law (1.4%).

Things that are troublesome

The most frequent responses for things that are troublesome were "physical changes (decline in muscle strength and limited joint ROM" (35.7%), followed by "pain" (31.4%), "parents" (20%), and then "limitations of ADL/IADL" and "difficulty moving" (both 18.6%). Only 1 patient listed bleeding.

Discussion

Hemophilia patients in middle and old age, who have experienced the time when there was no regular replacement therapy to suppress bleeding as can be done with current therapy, often have limited ROM, joint instability, joint contracture, muscle atrophy, and synovitis (*3*). This is the first multicenter study to investigate motor function and ADL in hemophilia patients with HIV infection. As of May 31, 2019, there are 6,596 hemophilia patients in Japan, 706 of whom are living with HIV infection due to receiving contaminated blood products (*6*). This study involved 70 patients, representing 10% of this population.

In a multicenter study, Siboni *et al.* investigated the elbow, knee, and ankle joint function of 39 middle aged and older hemophilia patients (mean age, 68 years; range, 65-78 years) (*12*) and found hemophilic arthropathy in 37 of the patients. Goto *et al.* also investigated joint function in 31 hemophilia patients (mean age, 38.3 years; range, 16-61 years) targeting the elbow, knee, and ankle joints and found end-stage arthropathy in 60.2% (*13*). Our study, which also included the shoulder and hip joints, showed that these joints and the elbow, knee, and ankle joints all had limited ROM. In particular, ankle dorsiflexion showed severely limited ROM at 10.4% of the reference value. The next most severely affected joint motions were hip abduction at 72.5% of the reference value and then shoulder abduction at 79.6%. Our study is the first to reveal limited ROM in the hip and shoulder joints.

Some previous studies have investigated muscle strength in patients with hemophilia (*13-15*) but were limited to the knee joint. The present study investigated muscle strength around the shoulder, elbow, hip, knee, and ankle joints, finding that decreased muscle strength was most frequently seen in ankle plantarflexion, followed by hip extension and hip abduction. The decline in muscle strength around the ankle joints was attributed to immobility of the joints caused by intra-articular bleeding (pain and swelling), given the severely limited ROM relative to the reference values of ankle dorsiflexion (10.4%) and plantarflexion (78.0%).

The decrease in hip joint ROM was attributed to pain and immobility caused by arthropathy, given that the flexion and extension ROM were 84.6% and 96.0% of the reference values, respectively.

Because bleeding is less common in the wrist joint compared with other joints in hemophilia (*16*), we did not include it in the evaluation of ROM or muscle strength in this study. However, grip strength is an index of muscle strength and is also correlated with cardiopulmonary function (*17*); thus, we evaluated grip strength as an index of general physical function in this study. The result showed that grip strength of the patients in their 30s was 83.5% of the reference value, which decreased with age. The grip strength of those in their 60s was 58.0% of the reference value, indicating deterioration of physical function with age. In a study by Goto *et al.* measuring grip strength, the mean value was 31.9 kg in patients with mean age of 38.3 years (*15*), which is lower than the mean grip strength of our patients in their 30s of 39.6 kg. The reason for the higher value of grip strength in our study is thought to be selection bias. The patients in the study by Goto *et al.* were outpatients, whereas our patients participated in the motor function, ADL, and IADL checkups that were held at patients' association meetings and thus could be presumed to have better motor function and to more actively exercise.

No conventional cross-sectional study of hemophilia patients has examined walking speed. Given that studies of healthy individuals and stroke patients have demonstrated the importance of being able to walk quickly to being able to walk practically (*18,19*), we evaluated fast walking. We found the proportions of patients in their 40s, 50, and 60s who could walk quickly were 85.5%, 78.2%, and 73.9% of the reference values, respectively. These data indicate practical walking ability may decrease with age in these patients. Knee flexion ROM, ankle dorsiflexion ROM, and hip extension muscle strength were identified as factors affecting walking speed. The hip extensor muscles play a role in supporting body weight from initial ground contact to mid-stance (*20*). Hip extensor muscle weakness was frequently seen in the patients in this study, suggesting that it may have also affected the walking speed.

Siboni *et al.* (*13*) and Stephensen *et al.* (*21*) have reported that muscular atrophy is present in hemophilia patients. However, no study has reported the four girth measurements that we examined in these patients, and both Canaro *et al.* (*2*) and Stephensen *et al.* (*22*) have pointed out that there has been no quantitative study of muscle atrophy. Here, we measured the girth of the upper arm, forearm, and lower leg and thigh, and compared the values with those of healthy individuals in 10-year age groups (*11*). The values were smaller in our patients than in healthy individuals at all measurement sites, and the difference was largest in the thigh. In addition, a notable finding was that the mean girth of the thigh in patients in their 50s and 60s was 38.5 cm and 37.2 cm, respectively, which was about the same as the standard values of healthy individuals.

Siboni *et al.* also evaluated ADL in a multicenter study (*13*) but did not evaluate items related to Japanese lifestyle. Therefore, we used a scale developed by Goto *et al.* (*7*). Many patients responded that movements requiring deep flexion or heavy loading of the lower limbs, such as "standing up from the floor", "squatting", "climbing up and down stairs", "sitting on the floor", and "walking on a slope" were either "difficult" or "cannot do", consistent with the results of Goto *et al.* (*14*) and Iwata *et al.* (*22*). More than 60% of the patients in the present study responded that the movements of "standing up from the floor" and "squatting" were "difficult" or "cannot do". The mean age of patients of this study was 52 years, which means that aspects of the Japanese lifestyle are difficult for these patients although they are only in their 50s.

Siboni *et al.* (*12*) examined IADL in patients with hemophilia, but their study was conducted outside Japan. In the present study, "putting away futons" was found to be the most difficult activity, revealing difficulty in Japanese lifestyle, as with ADL. Moreover, "laundry" and "cooking" were listed as difficult activities, showing that patients have difficulties in activities related to food, clothing, and housing, which are necessities of life.

In this study, we also included "self-injection", which is necessary for treatment, as an IADL item. The result showed that 14.3% of the patients answered that "self-injection" was "difficult" or "cannot do". As this patient population ages, it can be expected that ROM will worsen and presbyopia will develop, so the number of patients who have difficulties in "self-injection" may increase further in the future.

The results revealed that a "decrease in muscle strength and limitation of ROM" was the most frequent response, at 35.7%, for the most troublesome problem, followed by "pain" (31.4%). On the other hand, only 1 patient listed "bleeding". These results reflect that the problem of bleeding itself is being solved with advances in treatment methods, but that joint dysfunction and pain are issues that remain to be addressed.

The study showed that the person who mainly performs household tasks is someone other than the patient in more than half of the cases. Notably, for 12.9% of these patients, the primary helper was their parents. Given that "pain", "parents", and "limitation in ADL/IADL" were some of the most common problems, we can surmise that many patients have pain and rely on their parents for ADL/IADL.

Limitations

Some limitations of this study include that we are

unable to determine whether the decline in motor function revealed in this study was due to hemophilia or HIV infection. The reason for this is that the previous studies referred to in this report also included some hemophilia patients with HIV infection, ranging from 3.0% (*13*) to 38.7% (*14*), and it is not possible to compare our results with those of the previous studies with respect to the presence or absence of HIV infection. In addition, because the patients in this study voluntarily participated in patients' meetings where motor function, ADL, and IADL checkups were offered, our study population may have been biased toward patients with relatively good motor function and those who are proactive in maintaining or improving motor function. The patients in this study accounted for about 10% of hemophilia patients with HIV infection due to contaminated blood products in Japan. A study including all of these patients might show even greater impairment of motor function and ADL. Based on the above, it is necessary in the future to survey more patients with hemophilia and compare those with and those without HIV infection to accurately understand the condition of motor function and ADL/IADL in these patients.

Conclusion

Evaluation of hemophilia patients with HIV infection due to contaminated blood products who participated in checkups of motor function, ADL, and IADL that were held during patients' association meetings revealed that they had locomotor disorders, impairment in functions required for ADL, and pain even though they were fairly young, at a mean age of 52 years, and that they were in the worrying situation that maintenance of daily life may become difficult in the future depending on their parents' condition.

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