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Long-term impact of haemarthrosis on arthropathy and activities of daily living in Japanese persons with haemophilia

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David Stephensen
Editor-in-Chief, *Haemophilia*

Dear Dr. Stephensen;

Re: Manuscript reference *No. HAE-00384-2019*

Please find attached a revised version of our manuscript 'Long-term impact of haemarthrosis on arthropathy and activities of daily living in Japanese persons with haemophilia', which we would like to resubmit for publication as Letters to the editor in *Haemophilia*.
This article was described about the relationship between arthropathy and activities of daily living and once submitted in November 2019. After reviewing, this manuscript was recommended to be resubmit as letters to the editor.

The reviewers' comments were highly insightful and enabled us to greatly improve the quality of our manuscript.
In accordance with reviewers' suggestions, we have made the following changes:

1) We have revised and shortened the body of text, decreased references and tables to adopt the submission guidelines of letters to the editor.
2) According to the reviewers' indications, we have point-by-point responses to each of the comments of the reviewers. (see Response to the authors)

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in *Haemophilia*.

Word counts: Main body of text excluding references: 1359 words

We look forward to hearing from you at your earliest convenience.

Sincerely,

Teruhisa Fujii: M.D., Ph.D.

Title : Long-term impact of haemarthrosis on arthropathy and activities of daily living in Japanese persons with haemophilia

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Running title: Long-term impact of haemarthrosis on ADL

Word count: 1359 words

Dear Editor,

It has previously been reported that three or more haemorrhages in the same joint may induce haemophilic arthropathy [1]. However, the severity of haemophilic arthropathy may not depend on the number of haemarthrosis episodes alone, but may also be influenced by another factors, for example, the severity of bleedings and the patients' age at which coagulant factor concentrate administration is initiated, or initiation of prophylaxis. However, few reports have investigated these factors.

Most patients with haemophilia (PWH) with arthropathy are restricted during activities of daily living (ADL), such as walking [2], stair ascent or descent [3]. However, some PWHs with severe arthropathies can conserve the range of motion in affected joints, while other PWHs with less severe arthropathies experience difficulty in moving their joints and corresponding difficulty in performing ADLs. It is also unclear how the degree of difficulty in performing ADLs correlates with the severity of arthropathy in specific joints.

To clarify these two points, we conducted a questionnaire survey on the use of coagulant factor concentrates, symptoms of arthropathy, and ADLs in PWHs in Japan.

The survey was conducted at six institutions in Japan after being approved by the ethics committee in each institution. Patients were excluded if they were younger than 20 years of age or had mild haemophilia. All participants completed the questionnaire

anonymously and underwent radiographic examination of six index joints (bilateral elbows, knees, and ankles). The survey included questions on the type and severity of haemophilia, age at diagnosis, age at the start of coagulant factor concentrate use, prophylaxis, joint bleedings, degree of joint pain, and the degree of difficulty experienced during stair ascent and descent, and during walking. In questions about the subjects' childhood, we prepared several options as answers over a certain range and asked the subjects to choose one. The radiological severity of haemophilic arthropathy in each joint was evaluated using the Arnold–Hilgartner staging system (AHSS) [4], which was administered by orthopaedists experienced in using this system.

Questionnaire and radiographic data were collected anonymously from each of the six institutions and evaluated separately. The questionnaires were collated and evaluated at one university hospital, and radiological data were evaluated at another research facility.

A total of 79 sets of questionnaires and radiological data were analysed. These data were analysed statistically with Statcel 4 (OMS publishing, Tokyo, Japan), which is an add-in statistical software for Microsoft Excel. A value of $p<0.05$ was taken to indicate a statistically significant difference.

[Table 1]

The characteristics of the included PWHs are shown in Table 1. All PWHs were male, and the median age was 37 years (range 21–72 years). At the time of the survey, 30 patients were receiving prophylaxis that was almost secondary or tertiary, while only three were receiving primary prophylaxis. We abandoned our analysis of the relationship between "duration of prophylaxis" and hemophilic arthropathy because of the shortage of valid responses. Both descending and ascending stairs were more difficult lower limb activities than walking (Chi-square for independent values test, $p<0.001$).

Regarding haemarthrosis episodes, more PWHs experienced ankle bleedings (right 84.6%, left 78.2%) than elbow (right 62.8%, left 61.5%) or knee (right 58.9%, left 56.4%) bleedings (Chi-square for independent values test, $p<0.001$). However, there were no differences among the respective joints regarding the other survey items such as "age at first bleeding", "age at the most frequent bleeding", "duration of the most frequent bleeding", and "average bleeding during the past year". During times of non-bleeding, most PWHs felt pain during motion, while pain at rest was rarely reported.

After scoring the AHSS grades so that stage I equalled a score of 1 in all six joints in each participant, the scores were averaged for each joint. The average score of all participants was 3.177, and this correlated positively with age (Spearman's correlation coefficient test, $r=0.5290$, $p<0.001$) and the age at the initiation of coagulant factor concentrate infusions ($r=0.3740$, $p<0.01$). The results were similar when the AHSS grade was

analysed for each joint separately. Regarding the average AHSS score in each joint, the score for the ankle was higher than that for the knee or the elbow (Kruskal–Wallis test, $p<0.001$).

The relationship between bleeding episodes and the AHSS grade of each joint was also analysed. Single regression analysis was performed to analyse the relationship between the AHSS grade and the data on bleeding episodes. Higher AHSS grades were associated with younger age at first bleeding ($p<0.01$), more frequent bleeding episodes ($p<0.0001$), and a longer duration of bleeding episodes ($p<0.001$). Focusing on each joint individually, the AHSS grade in all joints was influenced by the "duration of the most frequent bleeding" item.

The relationship between the AHSS grade for elbows and the "carry baggage" item was analysed with the Spearman's correlation coefficient test and Fisher's exact probability test. In both statistical tests, the AHSS grade in each elbow was related to the "carry baggage" item ($p<0.001$ by Spearman's correlation coefficient test, $p<0.01$ by Fisher's exact probability test), and progression of the AHSS grade made it impossible to carry baggage.

The relationships between the AHSS grade in the lower limbs and ADL items were also analysed (Table 2). The Spearman's correlation coefficient test showed that "difficulty walking" was significantly affected by the AHSS grade in all joints, except for the right

ankle. Similarly, “difficulty descending or ascending stairs” became significantly more severe in accordance with the severity of the AHSS grade.

[Table 2]

Although several similar studies to this have previously been reported [5, 6], these either evaluated the relationship between the ability to perform ADLs and the severity or type of haemophilia, or compared the ADL ability of PWHs versus healthy control subjects. Subsequently, we decided to analyse the relationship between bleeding episodes and haemophilic arthropathies, and between the arthropathies and ADL impairments.

We used the AHSS for the radiographic evaluation of the patients’ joints. Although the World Federation of Hemophilia recommends the Pettersson scoring system for the radiographic classification of haemophilic arthropathy [7], this system has low interobserver reliability, whereas the AHSS has moderate reliability [8].

A limitation of our study is that answers to many questionnaire items depend upon PWH memories, or hearsays from their parents in some cases. Although questionnaire answers can be validated if all medical records are preserved, this is impossible in most cases. Therefore, for the questionnaire items on patient childhoods, we prepared several answered options over a certain range and asked the subjects to choose one of them. In this way, they could answer within a certain range without recalling the episodes accurately.

Considering our data, as the AHSS score increased, the ability to perform ADLs decreased. Regarding the lower limbs, the ability to perform ADLs related to walking and using stairs decreased in accordance with the severity of the AHSS grade. However, the ankle disability seemed to have a smaller influence on the AHSS grade than the knee disability. We speculate that this may be because Chopart or Lisfranc joints take the role of the ankle instead of the damaged joint, such that ankle arthropathy may have a smaller influence on walking and stair descent and/or ascent than knee arthropathy.

In conclusion, our study showed that PWHs who experienced repeated haemarthrosis over a certain period of time developed severe haemophilic arthropathies, which led to a decline in their ability to perform ADLs. It is important to initiate an effective prophylactic therapy at a young age to prevent repeated episodes of haemarthrosis.

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his colleagues evaluate radiographic data of the patients' joints. Both of FTs and TH revised the manuscript.

Disclosers: The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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Table 1. Characteristics of the survey participants

Parameter	n†
Type	A 63 B 16
Severity	Severe 62 Moderate 17
Age at diagnosis (y.o.)	0-5: 64 6-10: 9 11-15: 2 15-20: 1 >20 : 3
Age at beginning of factor concentrate use (y.o.)	0-5: 40 6-10: 15 11-15: 7 15-20: 6 >20: 11
Prophylaxis	Yes 30 No 48
Duration of Prophylaxis (y)	<2: 6 2-5: 1 6-10: 10 10<: 10 Unknown: 3
Participation in physical training at school	Almost 12 More than half 20 Less than half 13 Rare 32
History of sports	Yes 23 No 56
Difficulty walking‡	No 31 Mild 43 Moderate 11 Severe 3
Difficulty descending stairs§	No 28 Mild 15 Moderate 33 Severe 3
Difficulty ascending stairs§	No 36 Mild 12 Moderate 28 Severe 3
Carrying baggage in the right hand	Easy 53 Slightly difficult 17 Difficult 5 Impossible 4
Carrying baggage in the left hand	Easy 52 Slightly difficult 20 Difficult 5 Impossible 2

n†: number of valid responses; ‡mild: able to walk without a walking stick, moderate: unable to walk without a walking stick, severe: uses a wheelchair because of an inability to walk; §mild: able to ascend or descend while holding the rail, moderate: able to ascend or descend in a step-by-step manner while holding the rail, severe: unable to ascend or descend.

Table 2. The AHSS scores in the knees/ankles, and the ADLs related to the lower limbs

(a) Difficulty walking

	AHSS score	Right					Left				
		None	Mild	Moderate	Severe	p*	None	Mild	Moderate	Severe	p*
Knee	I	25	18	1	0	<0.001	22	16	2	1	<0.001
	II	1	0	0	0		0	0	0	0	
	III	1	2	0	1		3	0	1	0	
	IV	1	2	0	0		3	5	2	1	
	V	3	9	9	2		3	12	5	1	
Ankle	I	9	4	0	1	0.082	8	6	0	0	<0.05
	II	1	0	1	0		2	2	0	0	
	III	2	3	1	0		4	2	2	0	
	IV	8	8	2	1		8	6	2	0	
	V	11	18	6	1		9	17	6	3	

(b) Difficulty descending stairs

	AHSS score	Right					Left				
		None	Mild	Moderate	Severe	p*	None	Mild	Moderate	Severe	p*
Knee	I	26	13	7	0	<0.001	24	10	8	1	<0.001
	II	0	0	1	0		0	0	0	0	
	III	1	0	2	1		2	1	1	0	
	IV	1	1	1	0		1	1	8	1	
	V	1	0	21	1		1	3	17	0	
Ankle	I	9	4	2	0	<0.01	11	2	2	0	<0.001
	II	1	0	1	0		0	2	2	0	
	III	2	2	2	0		4	1	3	0	
	IV	8	3	8	1		5	6	6	0	
	V	8	6	21	1		8	4	21	2	

(c) Difficulty ascending stairs

	AHSS score	Right					Left				
		None	Mild	Moderate	Severe	p*	None	Mild	Moderate	Severe	p*
Knee	I	33	8	5	0	<0.001	29	7	6	1	<0.001
	II	0	0	1	0		0	0	0	0	
	III	1	0	2	1		3	0	1	0	
	IV	1	1	1	0		2	1	7	1	
	V	1	2	19	1		2	3	16	0	
Ankle	I	11	2	2	0	<0.01	12	1	2	0	<0.001
	II	1	0	1	0		0	2	2	0	
	III	3	1	2	0		5	0	3	0	
	IV	11	2	6	1		10	2	5	0	
	V	10	6	19	1		9	6	18	2	

AHSS: Arnold-Hilgartner staging system; ADLs: activities of daily living

The Arabic numerals in the columns represent the numbers of patients. *The p values were obtained from Spearman's correlation coefficient by rank test.