Table 1
Patient numbers for each MPS II type and the results of HSCT effectiveness.

	No. of patients			
	Type A	Type B	Type C	Type D
Retrospective study from transplant patient records (n = 21)	1	6	7	7
ADL (see Table 2)				
Patients analyzed (n = 13)	1	3	5	4
Patients stabilized/improved from baseline	1	2	3	4
IQ/DQ (see Table 2)				
Patients analyzed (n = 11)	0	2	4	5
Patients stabilized/improved from baseline	0	2	1	0
FIM (see Table 2)				
Patients analyzed (n = 11)	1	1	6	3
Patients stabilized/improved from baseline	1	1	2	1
Brain MRI (see Tables 2 and 3)				
Patients analyzed (n = 17)	1	6	5	5
Patients stabilized/improved from baseline (see Tables 2 and 3)	0	5	4	2
Cardiac valvular regurgitation (see Tables 2 and 4)				
Patients analyzed (n = 21)	1	6	7	7
Patients stabilized/improved from baseline	1	4	5	6
Family questionnaire analysis (n = 60)	7	13	26 (see Table 5)	14
HSCT (+) (n = 17); [no. rejected]	3 [1]	3 [1]	7	4
HSCT (−) (n = 43)	4	10	19	10

Abbreviations: ADL, activities of daily living; DQ, development quotient; FIM, functional independence measure; IQ, intelligence quotient; MRI, magnetic resonance imaging.

analyzed. The activity of iduronate 2-sulfatase in patient 1-3 showed the lower limit of normal activity, probably because of incomplete chimera. All other patients showed activity within the mean ± 1 SD of normal. Age at transplantation was 64.2 ± 30.2 months. The mean follow-up period was 115.7 ± 41.4 months. Patient numbers for each MPS II type and a brief summary of results for HSCT effectiveness are shown in Table 1.

Clinical background and outcome among HSCT-treated MPS II patients are detailed in Table 2. Not every patient underwent all clinical examinations. Answers to the questionnaire were obtained for the analysis of ADL (school status, movement and daily activities, conversation, and toileting) from 13 patients: Type A (n = 1), Type B (n = 3), Type C (n = 5), and Type D (n = 4). Two patients with attenuated forms of the disease (patients 1-3 and 7-3) maintained a normal level of ADL (Level A) for each item throughout the observation period. None of the patients with severe forms of the disease except two Type C patients (patients 5-1 and 1-1) showed deterioration from baseline status.

IQ/DQ data were available for 11 patients: Type B (n = 2), Type C (n = 4), and Type D (n = 5). Two Type B patients (7-3 and 7-2) showed an IQ within the normal range both at baseline and at the most recent assessment. Deterioration was observed in two Type C patients (5-2 and 7-6) and two Type D patients (7-4 and 12-1). One Type C (patient 5-1) and one Type D (patient 8-2) showed such severe deterioration at baseline that evaluation of change was not possible. One Type C patient (7-1) and two Type D patients (7-5 and 9-1), whose IQ/DQ were > 70 at baseline, maintained their developmental status without deterioration, while DQ decreased with increasing age (Table 2).

FIM score was available in 11 patients: Type A (n = 1), Type B (n = 1), Type C (n = 6), and Type D (n = 3). Patients with Type A/B disease maintained scores in the normal range. Three Type C/D patients (7-8, 7-1, and 4-1) showed disease attenuation in FIM score when compared with the natural history described in a previous report [14]. One Type C (patient 7-8) and one Type D (patient 4-1) showed disease attenuation in FIM score for motor function, while the score for cognition did not differ from untreated patients. One Type C (patient 7-1) showed disease attenuation in FIM scores for both motor function and cognition. Other patients with severe forms of the disease (4 Type C and 2 Type D) showed no difference as compared to the previously reported untreated patients [14]. The results are summarized in Table 2.

IQ/DQ and FIM scores were both obtained in seven patients: one Type B (patient 7-2), four Type C (patients 5-2, 7-6, 7-1, and 5-1), and two Type D (9-1 and 12-1). Among these patients with Type C/D disease and brain involvement, only one patient (7-1) showed disease attenuation in both FIM score and developmental status. The remaining three Type C patients showed no difference in FIM score as compared to natural history. While developmental status and ADL improved in patient 9-1, no efficacy in FIM score was shown as compared to natural history.

Brain MRI data were analyzed in 17 patients: Type A (n = 1), Type B (n = 6), Type C (n = 5), and Type D (n = 5) [Table 2]. Improvements in Categories I and III lesions were shown in nine (4 Type B, 2 Type C, and 3 Type D) and four patients (2 Type C and 2 Type D), respectively. Eight out of 17 patients (59%) had an improvement in total score. All of the six patients who showed an increase in total score had deterioration in Category IV lesions (brain atrophy). Three of these six patients had Type D disease (patients 7-4, 8-2, and 10-1). Two patients (7-1 and 4-1) who showed disease attenuation in FIM score also showed improvement in brain MRI abnormality scores. There was no difference in the effectiveness between the attenuated forms (Type A/B) and severe forms (Type C/D) of the disease or any correlation between the effectiveness of HSCT and age at HSCT, as summarized in Table 3.

Valvular regurgitation was analyzed for mitral, aortic, and tricuspid valves. Pulmonary valves showed insufficient lesions to warrant analysis. Twenty-one patients were analyzed: Type A (n = 1), Type B (n = 6), Type C (n = 7), and Type D (n = 7), i.e. a total of 63 valves. Results are summarized in Tables 2 and 4. Valvular regurgitation improved in 32% and stabilized in 56% of valves. There was no difference in efficacy between patients with the attenuated (Type A/B) and severe forms (Type C/D) of MPS II (data not shown). However, valvular regurgitation deteriorated more frequently in the patients transplanted at ≥ 6 years of age (5 valves out of 8 patients), as shown in Table 4.

The amount of urinary GAG was analyzed from urinary uronic acid concentrations. Mean urinary uronic acid concentrations in children ages 7–16 years were 18.0 ± 5.5 (n = 24) and 165.5 ± 77.9 (n = 9) mg/g creatinine for normal children and among untreated Types A–D MPS II patients, respectively. Urinary GAG in HSCT-treated MPS II patients was 24.8 ± 9.8 mg/g creatinine (n = 7, ages 9–17 years). Urinary GAG in ERT-treated patients with MPS II at Osaka City University Hospital was 37.6 ± 14.3 mg/g creatinine (n = 6, age 7–16 years).

3.2. Family questionnaire analysis

Answers to the questionnaire were collected for 60 patients with MPS II from 55 families. The numbers of HSCT-treated and HSCT-untreated patients were 17 and 43, respectively. As the questionnaire sheet was anonymous, we could not identify the patients analyzed in the clinical study described above. The patients were divided into Types A–D clinical forms (Table 1), as previously described. Six out of 20 Type A/B patients were treated by HSCT and two of them (one each with Types A and B) underwent rejection. Four of 14 Type D patients received HSCT. However, they showed deterioration before transplantation. We analyzed the efficacy of HSCT in 26 Type C patents with respect to disease progression by age at onset of speech deterioration, walking disability, and convulsion (Table 5). The numbers of patients in the HSCT-treated and HSCT-untreated cohorts were 7 and 19, respectively. Mean ages of these cohorts were 145.7 ± 67.8 and 142.7 ± 88.6 months, respectively.

Seven Type C patients underwent HSCT at a mean age of 65.9 ± 22.1 months (range, 44–111 months). Before HSCT treatment, the seven patients showed no difference in developmental milestones as compared to the 19 HSCT-untreated patients. At the time of survey, 12 out of 19 (63%) HSCT-untreated patients showed deterioration of

Table 2
Clinical background and outcome among HSCT-treated MPS II patients (n = 21).

Patient no.	Disease type	Age at HSCT	Donor	Protocol	Chimeric status	GVHD	Follow-up	ADL (pre/post), [n = 13]				IQ/DQ (developmental age)	
								School status	Movement and daily activities	Conversation	Toileting	Pre	Post
1-3	A	19 y 8 m	Unrelated BM	CY + BU + ATG	50	No	6 y 7 m	(A/A)	(A/A)	(A/A)	(A/A)	NA	
10-3	B	4 y 11 m	Unrelated CB	CY + TBI	100	No	7 y 1 m	NA	NA	NA	NA	NA	
7-3	B	5 y 5 m	Normal sibling	CY + BU + ATG	100	No	8 y 7 m	(A/A)	(B/A)	(A/A)	(A/A)	114 (normal)	102 (normal)
7-2	B	6 y 0 m	Normal sibling	BU + ATG	Mixed	No	10 y 11 m	NA	NA	NA	NA	99 (normal)	91 (normal)
8-1	B	9 y 5 m	Normal sibling	CY + BU	100	No	12 y 7 m	(E/E)	(E/E)	(B/B)	(E/E)	NA	
10-7	B	7 y 9 m	Carrier sibling	CY + BU + ATG	100	No	11 y 3 m	(A/A)	(A/A)	(A/A)	(A/A)	NA	
10-5	B	11 y 6 m	Unrelated BM	CY + TBI	90	Yes	6 y 6 m	(A/D)*	(B/B)	(A/A)	(A/A)	NA	
5-2	C	3 y 4 m	Normal sibling	CY + BU	100	No	7 y 4 m	(B/B)	(C/B)	(B/B)	(D/B)	53 (3 y 11 m)	NA
7-8	C	4 y 3 m	Unrelated BM	CY + BU + ATG	100	No	7 y 4 m	NA	NA	NA	NA	NA	
7-7	C	5 y 5 m	Unrelated CB	CY + BU + ATG	100	No	7 y 7 m	NA	NA	NA	NA	NA	
7-6	C	5 y 9 m	Carrier sibling	CY + BU + ATG	100	No	6 y 11 m	(B/B)	(C/C)	(D/C)	(D/B)	25 (1 y 8 m)	NA
7-1	C	7 y 0 m	Normal sibling	CY + BU	100	Yes	16 y 3 m	(B/B)	(B/A)	(B/A)	(E/E)	78 (5 y 6 m)	65 (9 y 6 m)
5-1	C	7 y 3 m	Normal sibling	CY + BU	100	No	10 y 5 m	(B/B)	(C/D)*	(C/C)	(B/C)*	NA	NA
1-1	C	9 y 4 m	Normal sibling	CY + BU	100	No	16 y	(C/D)*	(C/D)*	(C/D)*	(C/D)*	NA	
7-4	D	2 y 0 m	Unrelated BM	CY + BU + ATG	100	Yes	9 y 11 m	NA	NA	NA	NA	50 (1 y 0 m)	NA
7-5	D	2 y 2 m	Normal sibling	CY + BU + ATG	96	No	8 y 8 m	NA	NA	NA	NA	70 (1 y 6 m)	29 (2 y 2 m)
9-1	D	2 y 2 m	Unrelated BM	CY + BU + ATG	100	No	12 y	(E/B)	(C/A)	(B/A)	(C/A)	100 (2 y 2 m)	40 (5 y 6 m)
12-1	D	2 y 6 m	Normal sibling	CY + BU	100	No	8 y 3 m	(E/B)	(C/C)	(C/C)	(D/D)	66 (5 y 6 m)	30 (1 y 10 m)
8-2	D	2 y 9 m	Normal sibling	CY + BU	100	No	12 y 3 m	(D/B)	(D/D)	(D/D)	(D/D)	NA	NA
4-1	D	4 y 2 m	Unrelated BM	CY + BU + ATG	100	No	5 y 5 m	(B/B)	(A/A)	(C/B)	(D/B)	NA	
10-1	D	5 y 4 m	Normal sibling	CY + BU + ATG	100	No	7 y 8 m	NA	NA	NA	NA	NA	

Abbreviations: ADL, activities of daily living; ATG, antithymocyte globulin; BM, bone marrow; BU, busulfan; CB, cord blood; CY, cyclophosphamide; DQ, development quotient; FIM, functional independence measure; HSCT, hematopoietic stem cell transplantation; IQ, intelligence quotient; m, month; MPS, mucopolysaccharidosis; MRI, magnetic resonance imaging; NA, not available (not found, not examined, and/or not measurable); TBI, total body irradiation; y, year.

[a] Regression of level or score.

Table 2 (*continued*)

Patient no.	FIM	Brain MRI abnormality (pre/post) [n = 17]				Valvular regurgitation (pre/post) [n = 21]		
	Difference from natural history	Category I (cribriform change)	Category II (white matter signal change)	Category III (ventricular enlargement)	Category IV (brain atrophy)	Mitral	Aortic	Tricuspid
1-3	Normal range	(2/2)	(1/2)[a]	(2/2)	(1/2)[a]	II–III/IV	II/I	II–III/IV
10-3	Normal range	(1.5/0.5)	(0/0)	(1/1)	(0/0)	III/(−)	(−)/(−)	(−)/(−)
7-3	NA	(1/0.5)	(0/0)	(0/0)	(0/0)	I–II/(−)	II/(−)	(−)/(−)
7-2	Normal range	(1/0)	(0/0)	(0/0)	(0/0)	I–II/I–II	(−)/II[a]	I/(−)
8-1	NA	(1/1)	(2/2)	(1/1)	(0/0)	I/I	(−)/II[a]	I/I
10-7	NA	(3/2)	(0/0)	(0/0)	(0/0)	II/I	(−)/(−)	(−)/(−)
10-5	NA	(1/2)[a]	(0/0)	(0/1)	(0.5/1.5)[a]	I/I	II/II	(−)/(−)
5-2	No difference	NA	NA	NA	NA	(−)/(−)	(−)/(−)	(−)/(−)
7-8	Attenuation	(1/1)	(0/0)	(0/0)	(0/0)	I/I	(−)/(−)	I/I
7-7	NA	(1/0)	(1/0)	(1/0)	(0/0)	III/II–III	(−)/II[a]	I/(−)
7-6	No difference	(1/1)	(0/0)	(2/2)	(1/1.5)[a]	(−)/(−)	II/(−)	II/(−)
7-1	Attenuation	(1/0)	(0/0)	(2/1.5)	(1/1)	I/I	I/(−)	(−)/(−)
5-1	No difference	NA	NA	NA	NA	(−)/I[a]	II/I	(−)/(−)
1-1	No difference	(2/2)	(2/2)	(2/2)	(3/3)	I/II[a]	II/I	(−)/(−)
7-4	NA	(0.5/0)	(0/0)	(0/1)[a]	(0/1)[a]	II/I	II/I	I/(−)
7-5	NA	(1/0)	(0/0)	(0.5/0)	(0/0)	II/II	(−)/(−)	(−)/(−)
9-1	No difference	NA	NA	NA	NA	(−)/II[a]	I/I	(−)/(−)
12-1	No difference	NA	NA	NA	NA	(−)/(−)	(−)/(−)	(−)/(−)
8-2	NA	(2/2)	(1/1)	(1/2)[a]	(2/3)[a]	(−)/(−)	(−)/III[a]	I/(−)
4-1	Attenuation	(1/0.5)	(0/0)	(1/0.5)	(0/0)	(−)/(−)	I/I	(−)/(−)
10-1	NA	(0.5/0.5)	(0/0)	(3/3)	(2/3)[a]	(−)/(−)	(−)/(−)	(−)/(−)

Table 3
Effectiveness of HSCT on brain MRI lesions among MPS II patients according to age at transplantation or MPS II clinical classification.

	No. of patients					
	Age at HSCT				MPS II classification	
	<4 y (n=3)	4–5 y (n=3)	5–6 y (n=5)	>6 y (n=6)	Type A/B (n=7)	Type C/D (n=10)
Improved (n=8)	1	2	3	2	4	4
Stable (n=3)	0	1	1	2	1	2
Deteriorated (n=6)	2	0	2	2	2	4

Abbreviations: HSCT, hematopoietic stem cell transplantation; MPS, mucopolysaccharidosis, y, year.

speech, nine (47%) spoke no words, six (32%) had convulsions, and six (32%) did not walk. All but one of the HSCT-treated Type C patients showed no speech deterioration, loss of speech, or convulsions.

4. Discussion

We performed a retrospective study on the long-term efficacy of HSCT in MPS II patients. Efficacy was noted, to some extent, even with respect to brain involvement as long as HSCT was carried out before developmental delay became clinically manifest, without brain atrophy on MRI. The study of ADL from transplanted patient records showed that HSCT-treated patients maintained almost the same levels of speech ability and gait as at baseline or an improvement in most patients (Table 2). The questionnaire study among Type C patients of HSCT-treated and HSCT-untreated cohorts showed no deterioration in all except one Type C patient in the HSCT-treated cohort, which is different from the natural history of the disease (HSCT-untreated cohort) [Table 5]. However, no difference was shown in FIM score when compared to the natural history of the disease except for three patients (7-8, 7-1, and 4-1). Moreover, two patients with Type D disease (patients 7-5 and 9-1) with baseline DQ of 70 and 100, respectively, showed severe deterioration and no difference was shown with respect to the natural history of the disease for patient 9-1 with respect to FIM score. Thus, HSCT may not be effective with respect to brain involvement for Type D MPS II patients.

The effectiveness of HSCT on brain MRI was distinctive. Improvement in Categories I and III lesions was clearly shown. Category I lesions involve enlargement of perivascular spaces where GAG-loaded cells are accumulated and Category III lesions occur from insufficient cerebrospinal fluid absorption or secondarily from brain atrophy. It is speculated that engrafted cells migrate into perivascular and subarachnoid spaces and secrete the deficient enzyme responsible for diminishing GAG storage, thereby improving lesions. On the other hand, for Category IV lesions, which results from neuronal cell loss, deterioration was observed in six patients and none improved. It may be that engrafted cells are not located to deep brain tissue. Of these six patients, three were Type D patients and two of them showed a worsening of Category III lesions, which probably resulted from the progression of Category IV lesions (brain atrophy). Thus, the efficacy of HSCT is not shown in Type D patients from the brain MRI study.

Two patients with Type C/D disease (patients 7-1 and 4-1) showed effectiveness in both intellectual (ADL, IQ/DQ, and FIM) and imaging analysis (brain MRI), while three patients (patients 7-6, 7-4, and 8-2) showed deterioration in both. These three patients already had severe intellectual deterioration at baseline with low IQ/DQ. However, no clear correlation between the effectiveness on brain MRI lesions and on intellectual scores was shown in other Type C/D patients because of insufficient data.

The most serious cardiac consequence in MPS II is valvular insufficiency. Thickening of heart valves by GAG accumulation and fibrosis results in valvular stenosis and regurgitation, culminating in heart failure, which is one of the most frequent causes of death in MPS II patients in our experience. Mitral valves and aortic valves were those primarily affected in our patients. In particular, the aortic perivalvular area was enlarged in older patients and caused regurgitation. Eighty-eight percent of valves showed improvement (32%) or stabilization (56%) with respect to regurgitation. A deterioration of valvular regurgitation was frequently observed in older patients who received HSCT, who already had regurgitation on baseline examination prior to engraftment. We have experience with different patients in a family with Type B MPS II who received and did not receive HSCT in this study. An uncle did not receive any therapy, could not walk at 17 years, and died at 20 years from heart failure. His nephew was 18 years at survey (patient 10-7) and underwent HSCT at 7 years and 9 months old. Although he had mitral valve regurgitation, he remained relatively well and was practicing kendo in high school. The efficacy of HSCT on the respiratory system probably reduced his cardiac stress.

Table 4
Changes in cardiac valve involvement according to age at HSCT among MPS II patients.

	No. of patients with cardiac valvular regurgitation (n=21)				
	Age at HSCT				
	<4 y (n=6)	4–5 y (n=3)	5–6 y (n=4)	≥6 y (n=8)	Total (n=21)
Mitral valve (n=21)					
Diminished	1	1	2	3	7 (33%)
Stable	4 [3[a]]	2 [1[a]]	2 [2[a]]	3 [0[a]]	11 [6[a]] (52%)
Increased	1	0	0	2	3 (14%)
Aortic valve (n=21)					
Diminished	1	0	2	4	7 (33%)
Stable	4 [3[a]]	3 [2[a]]	1 [1[a]]	1 [0[a]]	9 [6[a]] (43%)
Increased	1	0	1	3	5 (24%)
Tricspid valve (n=21)					
Diminished	2	0	2	2	6 (29%)
Stable	4 [4[a]]	3 [2[a]]	2 [2[a]]	6 [5[a]]	15 [13[a]] (71%)
Increased	0	0	0	0	0 (0%)
Total (n=63)					
Diminished	4	1	6	9	20 (32%)
Stable	12 [10[a]]	8 [5[a]]	5 [5[a]]	12 [6[a]]	35 [25[a]] (56%)
Increased	2	0	1	5	8 (13%)

Abbreviations: HSCT, hematopoietic stem cell transplantation; MPS, mucopolysaccharidosis; y, year.
[a] Number with absence of regurgitation at HSCT (baseline).

Table 5
Clinical course of HSCT-untreated and HSCT-treated Type C MPS II patients in questionnaire analysis.

	Pre-treatment in HSCT-treated cohort (n=7)	HSCT-untreated cohort (n=19)
Mean ± SD age at developmental milestones (m)		
Speak words	17.1 ± 4.1	18.0 ± 6.3
Speak sentences	32.0 ± 9.2	40.1 ± 14.2
Age when noticed developmental delay (m)	26.4 ± 16.6	34.2 ± 12.5
Mean ± SD age at HSCT (m)	65.9 ± 22.1	–
Mean ± SD age at survey (m)	145.7 ± 67.8	142.7 ± 88.6

Disease progression	Post-treatment in HSCT-treated cohort		HSCT-untreated cohort	
	No. of affected (%)	Age when noticed (m)	No. of affected (%)	Mean ± SD age when noticed (m)
Speech deterioration	1*/7 (14%)	42	12/19 (63%)	113.5 ± 40.4
Loss of speech	1*/7 (14%)	72	9/19 (47%)	150.4 ± 55.1
Convulsions	1*/7 (14%)	125	6/19 (32%)	186.0 ± 71.2
Unable to walk	0/7 (0%)	–	6/19 (32%)	186.5 ± 52.9

1*. The same patient.
Abbreviations: HSCT, hematopoietic stem cell transplantation; m, month; MPS, mucopolysaccharidosis; NA, not applicable; SD, standard deviation.

It is known that the efficacy of HSCT is affected by the transplantation condition. TBI can sometimes result in brain atrophy or dementia after many years delay. Since none of the Type C/D patients received TBI as part of their transplantation protocol, their deterioration must have resulted from the disease itself and not a consequence of TBI. It has been recently reported that lower enzyme activity after HSCT results in lower efficacy in the patients with MPS I severe form (Hurler syndrome) in a multicenter survey study of 197 patients [17]. In our study, two patients showed extremely low enzyme activity after HSCT. However, it is unclear whether they had poor efficacy from HSCT.

ERT has recently become available in Japan. It has demonstrated clear efficacy with respect to visceral organ involvement and urinary GAG secretion [9,10]. ERT is superior to HSCT in terms of safety and availability. However, ERT requires weekly injection, its cost is high, and antibody development is another problem. Moreover, the efficacy of ERT has not been clearly demonstrated with respect to brain [11,12] or heart valve involvement.

In patients who received HSCT, urinary GAG concentration was definitely decreased after engraftment. Values became almost the same as those of normal children. In ERT-treated MPS II patients, however, urinary GAG concentration was slightly higher than that in HSCT-treated patients. Similar results have been previously reported in patients with MPS I [4]. It is possible that engrafted cells provide the deficient enzyme more efficiently to the affected cells and organs than by systemic ERT administration.

In contrast to the efficacy of HSCT with respect to MRI findings, our personal experience with ERT of six patients aged 1–12 years with severe MPS II showed a 4%–12% brain volume reduction following 2 years' treatment (data not shown). Moreover, none of them showed any improvement in any MRI lesion category. However, Wang et al. [18] reported that ERT reduced or stabilized brain MRI abnormalities. Longer observation periods are necessary to evaluate the efficacy of ERT on ADL, and heart and brain involvement.

Our study showed an improvement of brain MRI findings in HSCT-treated patients. We speculate that the efficacy is due to migrated microglial cells derived from donor cells. In 2009, Araya et al. [19] reported the localization of donor cells in the brain of a patient with MPS II after cord blood cell transplantation. Several studies have shown the migration of transplanted bone marrow cells into brain tissue [20,21]. In a recent report, autologous cord blood infusion showed some efficacy in children with acquired neurologic disorders [22]. It is known that HSCT shows efficacy on brain involvement in patients with genetic leukodystrophies including adrenoleukodystrophy, metachromatic leukodystrophy, and globoid cell leukodystrophy [23], and HSCT is a standard therapy for these patients in early stages of the disease. HSCT combined with gene therapy (ex vivo gene therapy) using a lentiviral vector has recently been shown to be successful in two patients with adrenoleukodystrophy [24]. It is speculated that stem cells can migrate across the blood–brain barrier in some situations such as the environment induced by disease.

On the other hand, the efficacy of HSCT on IQ/DQ was unclear in patients with MPS II. However, it can be concluded that the disease of lesser severity and an earlier time of transplantation will lead to better efficacy on IQ/DQ.

The disadvantages of HSCT are the mortality (11.5% in 1990–2003) and morbidity associated with the transplantation procedure [25]. Suitable donors may not be found easily and quickly. However, once engraftment has been established, the quality of life of patients will be better than in patients receiving weekly ERT treatment. Moreover, the expense of HSCT is less than that for ERT. HSCT also improves morbidity in patients with MPS II, particularly when performed early in the course of the disease. Exogenous ERT is unable to correct cognitive and CNS disease because of its inability to cross the blood–brain barrier. In contrast, HSCT allows donor-derived, enzyme-producing cells to migrate into the brain and other organs, thereby providing a permanent form of enzyme replacement [26,27]. The utility of HSCT should therefore be re-evaluated in the treatment for MPS II. HSCT is a worthwhile treatment for MPS II when it is performed before signs of brain atrophy appear on MRI and before heart valvular regurgitation appear. Therefore, neonatal screening for MPS II may result in improving of the prognosis. In the future, genetically engineered bone marrow cells, autologous cord blood cells, or other cells may become good sources for cell transplantation, or other novel intervention for genetic diseases may be developed.

Conflict of interest

Each author declares no potential conflict of interest, real or perceived.

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Original Article

Fatigue in survivors of childhood acute lymphoblastic and myeloid leukemia in Japan

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Abstract ***Background***: Fatigue in cancer survivors is a serious problem in pediatric oncology, but reports on this issue are limited, especially in Asian countries.

Methods: Sixty-three patients with acute lymphoblastic leukemia and 18 patients with acute myeloid leukemia who attended a follow-up outpatient clinic were enrolled. Participants were required to be >8 years of age, in remission, and without any cancer treatment for at least the previous 1 year. A control group consisted of 243 subjects whose age and gender were matched with the patient group. A questionnaire consisting of 12 items was devised for fatigue measurement.

Results: Principal factor analysis identified three dimensions, defined as physical fatigue, decreased function, and altered mood. The mean total and the three fatigue dimension scores tended to be higher in the control group, but significant differences between the scores were seen only in the total and physical fatigue scores. Multiple regression analysis indicated an association of present older age or shorter duration after completion of treatment with total and physical fatigue, and an association of presence of total body irradiation with decreased function.

Conclusion: Pediatric leukemia survivors in Japan experience equal or less fatigue compared with that of controls in different fatigue dimensions. Elucidation of underlying mechanisms of cancer-related fatigue including the differences of cultural background among different countries is necessary for future study of this issue.

Key words acute lymphoblastic leukemia, acute myeloid leukemia, cancer survivor, fatigue, questionnaire.

Fatigue is one of the serious complications of various cancers. Fatigue is a very subjective complaint, and has been shown to contain multidimensional symptoms, including physical, psychological, and emotional aspects.[1,2] Previous studies have indicated that cancer-related fatigue in children occurs during treatment,[3–5] at the end-stage of cancer,[6] and after completion of treatment.[7–12] In a review of cancer-related fatigue in adults, Servaes *et al.* cited several articles reporting an increased prevalence of "off-therapy fatigue", although the studies were based on different questionnaires and were sometimes conducted without any comparative studies using healthy subjects.[1] They also mentioned contradictory studies showing that intensity of fatigue in cancer survivors, especially after radiotherapy, was not significantly different from that in healthy controls. Zeltzer *et al.* reviewed the psychological status of children, including fatigue in childhood cancer survivors, based on a large-scale, long-term study of the Childhood Cancer Survivors Study.[13] They demonstrated that childhood cancer survivors were relatively healthy, both physically and emotionally, compared with their siblings. Survivors of bone tumors or brain tumors, however, were found to have more complaints of fatigue.[11,12] Because the articles cited in that review were from only Western countries, similar studies on that issue in Asian countries are highly warranted. The aim of the present study was therefore to examine the fatigue status of leukemia survivors in Japan, where several types of late effects other than fatigue have already been reported in long-term childhood cancer survivors.[14]

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Methods

Patients

Ninety patients with leukemia (acute lymphoblastic leukemia [ALL], $n = 69$; acute myeloid leukemia [AML], $n = 21$) who had been treated at each of eight hospitals and attended at a follow-up clinic for a routine check-up were initially enrolled. These patients had to meet the following criteria: (i) >8 years of age; (ii)

Table 1 Patient characteristics

n (%)	81 (100)
Gender	
Male	47 (58.0)
Female	34 (42.0)
Diagnosis	
ALL	63 (77.8)
AML	18 (22.2)
Present age (years)	
Mean ± SD	14.1 ± 5.7
8–11	30 (37.0)
12–14	20 (24.7)
15–17	12 (14.8)
18–29	19 (23.5)
Age at diagnosis (years)	
Mean ± SD	6.7 ± 3.5
0–2	20 (24.7)
3–5	21 (25.9)
6–9	15 (18.5)
10–15	25 (30.9)
Duration after completion of treatment (years)	
Mean ± SD	5.8 ± 3.8
0–2	12 (14.8)
3–5	36 (44.4)
6–9	22 (27.2)
10–20	11 (13.6)
Treatment	
Chemotherapy only	45 (55.6)
Chemotherapy + radiation†	8 (9.9)
Chemotherapy + SCT	10 (12.3)
Chemotherapy + radiation‡ + SCT	18 (22.2)

†Radiation includes only cranial irradiation; ‡radiation includes both cranial and/or total body irradiation.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; SCT, stem cell transplantation (done without irradiation)

in remission; and (iii) without any cancer treatment for at least the previous 1 year. Only those who completed questionnaires without any missing answers were included in the analysis, and termed as "leukemia survivors" hereafter. After excluding patients by the aforementioned criteria, 81 patients (ALL, $n = 63$; AML, $n = 18$) were finally included in the present study. Demographic and disease characteristics are summarized in Table 1. Healthy subjects were recruited either from among students at elementary, junior high school or senior high school enrolled in our previous study,[15] or from newly enrolled students and workers at Nara Women's University for the present study. Among a total of >1000 subjects, 243 were randomly selected to form the control group of age- and gender-matched subjects with the patient group. In order to construct an age- and gender-matched control group, we selected three healthy subjects of the same gender and approximately the same age for each patient. Because the number of healthy male subjects >20 years old was limited, female subjects were chosen instead in some cases. Therefore, the resulting average age and male/female ratio in the control group was slightly different, albeit statistically not significantly, from those of the patient group. This project was approved by the ethics and epidemiological committee at Nara Women's University .

Questionnaire for the evaluation of fatigue status

We devised our own questionnaire consisting of 12 items (Appendix I). The patients were asked to fill out the questionnaire at the hospital by recalling fatigue status during the most recent month. Each item was scored from 0 to 3: 0, not at all; 1, a few times per month; 2, a few times per week; 3, almost every day. The scores given by the patient were then summed to calculate the total fatigue scores (range: 0–36). An oblique rotation (direct oblimin) was used to determine the factor structures of the questionnaire. Three dimensions termed "physical fatigue", "decreased function", and "altered mood" were extracted, which accounted for 64.5% of the total variance. Items loaded in each factor are listed in Table 2. Convergent validity was evaluated in comparison with The Chalder scale[16] by using total scores in the control group. The internal consistency (Cronbach's α) was evaluated in both the patient and control groups.

Statistical analysis

Differences in gender and age distribution between the patient and control groups were analyzed using chi-squared test and Mann–Whitney test, respectively. Differences of fatigue scores between the two groups were examined on Mann–Whitney test. Multiple regression analysis was performed to define the association of present age, gender, diagnosis (ALL or AML), presence or absence of radiation therapy (cranial or total body irradiation), and duration after completion of cancer treatment with various types of fatigue. $P < 0.05$ was considered significant. All statistical analyses were carried out on a personal computer using StatMate version 3 (ATMS, Tokyo, Japan).

Results

Questionnaire reliability and validity

Because we devised our own questionnaire, we first evaluated the reliability and the validity of the questionnaire. Cronbach's

Table 2 Factor analysis of fatigue questionnaire used in the present study

Items	Factors		
	A	B	C
1. Feel tired	0.709	0.145	0.146
5. Want to lie down	0.696	0.275	0.091
8. Forceless	0.678	0.129	0.231
2. Still tired after night's sleep	0.572	0.275	0.008
12. Lack of energy	0.251	0.718	0.119
6. Make easy mistakes	0.106	0.651	0.067
11. Sleepy in the daytime	0.256	0.495	–0.064
3. Unrefreshing wake-up	0.082	0.491	0.134
9. Lack of concentration	–0.021	0.157	0.626
7. Irritated	0.182	0.098	0.617
4. Anxious about the body	0.175	–0.072	0.509
10. Depressed	0.218	0.173	0.452
Correlation between factors	A	B	C
A	1		
B	0.149	1	
C	0.257	0.215	1

A, physical fatigue; B, decreased function; C, altered mood.

Table 3 Fatigue scores

	Patients	Controls	*P*
n	81	243	
Present age (years) (mean; median)	14.1; 13	13.1; 12	0.18†
M/F (ratio)	47/34 (1.38)	136/107 (1.27)	0.79‡
Fatigue scores (mean; median)			
Physical fatigue	3.5 (3)	4.2 (4)	<0.05†
Decreased function	3.7 (3)	4.2 (4)	0.084†
Altered mood	2.6 (2)	2.9 (3)	0.31†
Total	9.8 (9)	11.4 (10)	<0.05†

†Mann–Whitney test; ‡chi-squared test.

α for the total and each of the three fatigue dimension scores was between 0.75 and 0.88 in both the patient and control groups. These values (i.e. >0.7) are considered to indicate good internal consistency. Next, we evaluated the reliability of the questionnaire by comparing total fatigue scores in the control subjects with the subscales in the Chalder scale.[16] The correlation coefficient between the questionnaire and the Chalder scale was 0.89, supporting the construct validity of the questionnaire.

Comparison of fatigue between leukemia survivors and controls

Mean total fatigue scores were significantly lower in leukemia survivors than in the age- and gender-matched controls (Table 3). Each of the three fatigue dimensions identified on factor analysis tended to be higher in the control group, but significant statistical difference was found only for the physical fatigue dimension.

Multiple regression analysis of fatigue in leukemia survivors

Table 4 shows that present older age was significantly associated with total and physical fatigue. Duration after completion of treatment was also associated with total and physical fatigue. Namely, these fatigue scores were found to decline with increased time after completion of treatment. Presence of total body irradiation was associated with the decreased function, but gender, diagnosis (ALL or AML), and cranial irradiation were not predictors of any type of fatigue.

Discussion

Because fatigue is a subjective complaint, a self-reported questionnaire is widely used for the assessment of fatigue in a selected group of cancer patients. The lack of universally acceptable instruments for such measurement, especially in children, makes the comparison difficult among different reports. Questionnaires that have been developed and validated originally to measure fatigue in the general population were mostly used for estimating cancer-related fatigue.[16–18] Some researchers have developed their own questionnaires for the assessment of cancer-related fatigue specifically.[19–23] We felt that some of these questionnaires were complicated to answer for young children, and there was the added difficulty of translating each item into Japanese accurately. Therefore, we developed our own questionnaire consisting of 12 items, and it demonstrated good validity and reliability.

The present finding that childhood leukemia survivors had equal or less fatigue compared with that of their age- and gender-matched controls in multidimensional aspects of fatigue is surprising. It is common for physicians to encounter complaints of severe fatigue in a subset of childhood cancer survivors in their daily practice. Furthermore, previous studies indicated increased fatigue in survivors of various childhood malignancies.[11,12] There have been, however, several reports that are in line with the present study. In the first large study of young adult survivors of childhood ALL, survivors were found to have less fatigue, but greater negative mood such as depression, anger, and confusion, than their siblings.[7] Langeveld *et al.* have reported that long-term survivors of various childhood cancers had less general fatigue and reduced motivation, but higher mental fatigue than controls without any history of cancer.[9] In a study of 161 long-term survivors of childhood ALL using the Revised-Piper Fatigue Scale, the prevalence of fatigue fell within the general population normal limits.[10] As one possible explanation for these results, there is the possibility that patients who received extensive chemotherapy for a long time may change their standard of fatigue,

Table 4 Demographic or treatment-related factors for fatigue (multiple regression analysis)

	Total	Physical fatigue	Decreased function	Altered mood
Present age (years)	0.24*	0.25**	0.04	0.05
Gender	0.35	0.26	−0.76	0.87
Diagnosis	−0.02	0.02	0.15	−0.25
Cranial irradiation	−0.04	0.62	−0.66	0.02
Total body irradiation	2.72	0.39	1.81*	0.54
Duration after completion of treatment (years)	−0.45*	−0.25**	−0.06	−0.15

*$P < 0.05$; **$P < 0.01$. Data given as β coefficients.

and thereby underestimate the fatigue during their time off therapy. This phenomenon is termed a "response shift".[9,24]

The following issues should be taken into consideration when interpreting the present results. First, development and use of our own questionnaire for fatigue evaluation has limitations. Convergent validity was evaluated in comparison with the Chalder scale[16] in the control group, but not in the patient group. Furthermore, using the present questionnaire made it difficult to compare our results with the previous reports. Recently, Kobayashi *et al.* reported on the reliability and validity of the Japanese-language version of the PedsQL multidimensional fatigue scale.[25] This questionnaire may become a good tool for comparison. Second, information on other late effects commonly seen in cancer survivors was lacking in the present study. Previous studies indicated the association of fatigue with the occurrence of late effects including congestive heart failure, pulmonary fibrosis, and endocrine disorders.[12,26] Finally, the average time after completion of cancer treatment was 5.8 years in the present study, which was shorter than that of previous studies.[9,10] The effect of duration without any cancer treatment on the intensity of fatigue is controversial. In breast cancer survivors, for example, it has been reported that post-treatment fatigue usually occurs up to 5 years after completion of adjuvant therapy.[27] In contrast, Mulrooney *et al.* noted the possibility that fatigue levels may decline over time during the long follow up of childhood cancer survivors.[26] Notably, the present study also demonstrated decrease in the total and physical fatigue scores with time after completion of treatment. For clarification of this issue, a further follow up of the fatigue status in the present cohort is necessary.

In spite of the aforementioned problems, we still believe that the present study is worthwhile for the following reasons. First, this study was done in comparison with healthy controls using the same questionnaire. Most previous studies were carried out either without healthy controls[9,12] or with patients' siblings as the control.[7] Second, this study might be the first childhood investigation on fatigue in leukemia survivors in Asian countries. Notably, we can find only one report on fatigue in pediatric oncology patients from Asian countries, but the report dealt with patients during chemotherapy.[5] In adults, several investigations reported a role of ethnicity in both chronic fatigue syndrome[28] and cancer-related fatigue.[29,30] Whether or not ethnicity has an effect on fatigue status in childhood cancer survivors is an issue for further investigation.

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APPENDIX I

Please score elements from 0 to 3 in boxes as the average for the past 1 month. (0, not at all; 1, a few times per month; 2, a few times per week; 3, almost every day)

1. ( ) How often do you feel tired?
2. ( ) How often do you feel still tired in the morning after night's sleep?
3. ( ) How often do you experience unrefreshing wake-up?
4. ( ) How often do you feel anxious about your body?
5. ( ) How often do you want to lie down in the daytime?
6. ( ) How often do you make easy mistakes?
7. ( ) How often do you feel irritated without any reason?
8. ( ) How often do you feel yourself forceless?
9. ( ) How often do you feel lack of concentration?
10. ( ) How often do you feel depressed without any reason?
11. ( ) How often do you feel sleepy in the daytime?
12. ( ) How often do you feel lack of energy?