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[学会等での講演、発表]

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［患者会への情報提供］

◎１．**加藤俊一**．造血幹細胞移植（移植医の立場から）．第1回先天代謝異常症患者会フォーラム．東京、2012年8月5日

◎２．**酒井規夫**．造血幹細胞移植（代謝専門医の立場から）．同上．

◎３．**笠原群生**．肝臓移植（移植医の立場から）．同上

◎４．**遠藤文夫**（代謝専門医の立場から）．同上

◎５．**遠藤文夫**．先天代謝異常症患者会による患者登録制度の構築．同上

◎６．Samantha Parker．欧州における尿素サイクル異常症患者家族会の活動について．同上

◎７．高柳正樹．わが国の先天代謝異常症患者家族会の現状について．同上．

◎８．**奥山虎之**．厚生労働省難治性疾患等克服研究事業における臨床情報バンクの設立．同上．

Ⅳ. 参考資料

Molecular Genetics and Metabolism 107 (2012) 513–520

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Long-term efficacy of hematopoietic stem cell transplantation on brain involvement in patients with mucopolysaccharidosis type II: A nationwide survey in Japan

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ARTICLE INFO

Article history:
Received 1 September 2012
Accepted 1 September 2012
Available online 7 September 2012

Keywords:
Hematopoietic stem cell transplantation
Mucopolysaccharidosis type II
Brain efficacy
Survey

ABSTRACT

Hematopoietic stem cell transplantation (HSCT) has not been indicated for patients with mucopolysaccharidosis II (MPS II, Hunter syndrome), while it is indicated for mucopolysaccharidosis I (MPS I) patients <2 years of age and an intelligence quotient (IQ) of ≥70. Even after the approval of enzyme replacement therapy for both of MPS I and II, HSCT is still indicated for patients with MPS I severe form (Hurler syndrome). To evaluate the efficacy and benefit of HSCT in MPS II patients, we carried out a nationwide retrospective study in Japan. Activities of daily living (ADL), IQ, brain magnetic resonance image (MRI) lesions, cardiac valvular regurgitation, and urinary glycosaminoglycan (GAG) were analyzed at baseline and at the most recent visit. We also performed a questionnaire analysis about ADL for an HSCT-treated cohort and an untreated cohort (natural history). Records of 21 patients were collected from eight hospitals. The follow-up period in the retrospective study was 9.6 ± 3.5 years. ADL was maintained around baseline levels. Cribriform changes and ventricular dilatation on brain MRI were improved in 9/17 and 4/17 patients, respectively. Stabilization of brain atrophy was shown in 11/17 patients. Cardiac valvular regurgitation was diminished in 20/63 valves. Urinary GAG concentration was remarkably lower in HSCT-treated patients than age-matched untreated patients. In the questionnaire analysis, speech deterioration was observed in 12/19 patients in the untreated cohort and 1/7 patient in HSCT-treated cohort. HSCT showed effectiveness towards brain or heart involvement, when performed before signs of brain atrophy or valvular regurgitation appear. We consider HSCT is worthwhile in early stages of the disease for patients with MPS II.

1. Introduction

Hematopoietic stem cell transplantation (HSCT) is a standard therapy for young patients with mucopolysaccharidosis I (MPS I, Hurler syndrome, OMIM 607014) [1–4]. HSCT is indicated when MPS I patients are <2 years of age and show an intelligence quotient (IQ) of ≥70. However, HSCT has not been indicated for patients with mucopolysaccharidosis II (MPS II, Hunter syndrome, OMIM 309900) as no obvious efficacy has been shown on the brain involvement of MPS II patients [5–8].

Abbreviations: ADL, activities of daily living; DQ, development quotient; ERT, enzyme replacement therapy; FIM, functional independence measure; GAG, glycosaminoglycan; HSCT, hematopoietic stem cell transplantation; IQ, intelligence quotient; JSPH, Japanese Society for Pediatric Hematology; MPS, mucopolysaccharidosis; MRI, magnetic resonance imaging; SD, standard deviation.

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1096-7192/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ymgme.2012.09.004

Enzyme replacement therapy (ERT) for MPS II was approved in the USA and Europe in 2006, and in Japan in 2007. Its efficacy has been demonstrated for visceral organ and soft connective tissue involvement [9,10], but poor or no efficacy was observed for brain involvement [11,12] because of poor penetration across the blood–brain barrier. Poor efficacy has also been speculated towards hard connective tissues such as bone and heart valves because of poor vascularity. Moreover, weekly injection can prove inconvenient to patients and their families, and the high cost of treatment is another issue to be taken into consideration.

MPS II is the most frequent type of MPS in Asian patients, accounting for 60% of all MPS types in Japan. Before the approval of ERT, HSCT was indicated for MPS II as a standard therapy in Japan. The efficacy of HSCT on visceral organs was clear and similar to that of ERT [13]. However, efficacy on the brain or heart valves has not been clearly evaluated for either ERT or HSCT.

We present the results of a retrospective evaluation of the efficacy of HSCT on MPS II by collecting the clinical records of the patients with MPS II who received HSCT from 1990 to 2003. We also analyzed the answers to a questionnaire given to two cohorts: HSCT-treated and HSCT-untreated (natural history) MPS II patients.

2. Methods

2.1. MPS II classification

Disease severity was evaluated in all patients into four types (A–D) on the basis of chronological development, history of disease onset, initial symptoms, and clinical records before transplantation. Because of the wide spectrum of clinical phenotypes in MPS II, it is important to compare patients within the same type of disease for the evaluation of efficacy. Types A and B are attenuated forms with normal intelligence, while Types C and D are severe forms with mental impairment. MPS II was classified as follows:

- Type A is the most attenuated form. Onset is at school age with joint stiffness. Patients show normal intelligence, can go to and learn at a normal school, and work.
- Type B shows onset before school age with joint stiffness and/or abdominal distension. They show normal intelligence in primary school but hearing and physical impairments may impact development to a low degree in high school.
- Type C is a severe form. The abnormality is noted at ≥2 years of age. They start to speak words at 12–18 months of age and speak sentences at 2–3 years of age. Developmental delay and abnormal features become obvious after 3 years of age.
- Type D is a most severe form. The abnormality is noted at <2 years of age. Abnormal features are obvious around 1 year of age. Speech is definitely delayed. They start to speak words at ≥2 years of age (or may not speak), but sentences are never spoken.

2.2. Retrospective study from transplanted patients' records

This study was approved by the HSCT committee the Japanese Society of Pediatric Hematology (JSPH) and the ethics committees of the participating institutes.

A questionnaire was sent to 12 transplant centers in Japan to ask whether they had any type of MPS patients who had received HSCT and were surviving with donor cell engraftment and complete or incomplete chimera. We then mailed the physicians in charge of the patients with MPS II to obtain informed consent from the patients and/or their guardians so that data could be collected from their clinical records.

School status, movement and daily activities, conversation, and toileting were graded into Levels A (independent), B (assisted occasionally), C (assisted in every event), and D (bedridden, lack of communication, or wholly assisted) for each item from questionnaires and/or clinical records. Data on intelligence quotient (IQ) and development quotient (DQ) were also collected from clinical records. Functional independence measure (FIM) score was also analyzed and compared with the natural history of the disease as described in a previous report [14].

Brain magnetic resonance imaging (MRI) abnormalities were classified into four distinct types (Categories I–IV) and graded by scores according to a previous report [15]. The score was judged by two pediatricians and one radiologist. The categories were as follows:

- Category I. Cystic or cribriform lesions were graded from T1-weighted MRI as follows: 0 = none; 1 = mild (≤10 cystic lesions<3 mm); 2 = moderate (>10 small cystic lesions of<3 mm); and 3 = severe (many cystic lesions including those >3 mm).
- Category II. White matter signal changes observed on T2-weighted MRI were graded as follows: 0 = none; 1 = mild (a few limited to the periventricular area); and 2 = severe (in most parts of the periventricular area and other white matter areas).
- Category III. Ventricular enlargement was graded as follows: 0 = none; 1 = mild (<3 mm widening of the third ventricle without temporal horn dilatation); 2 = moderate, (>5–10 mm widening of the third ventricle); and 3 = severe (>10 mm dilatation of the third ventricle with bulbous configuration).
- Category IV. Brain atrophy was graded as follows: 0 = none, 1 = mild (mild widening of Sylvian and interhemispheric fissures by <3 mm, but not all of the sulci are involved); 2 = moderate (widening of all fissures and sulci by 3–5 mm); and 3 = severe (widening of all fissures and sulci by >5 mm with definite loss of cortex and white matter).

Cardiac valvular regurgitations were analyzed by color Doppler echocardiogram with each valve graded according to severity into four levels (I–IV) by the Sellers' classification [16].

Urinary glycosaminoglycan (GAG) was analyzed as the amount of uronic acid. These data were compared with the values in HSCT-untreated MPS II patients and also with those in ERT-treated MPS II patients.

2.3. Family questionnaire analysis

We sent a questionnaire to each of the 60 families with 66 MPS II patients registered with "the Japanese MPS Family Society". Information was collected about chronological development and course of deterioration for both HSCT-treated and HSCT-untreated (natural history) patients. Patients were first classified according to MPS II Types A–D on the basis of information on chronological development, before HSCT if performed, and at disease onset. Data were compared between HSCT-treated and HSCT-untreated patients for MPS II Type C or D patients.

3. Results

3.1. Retrospective study from transplanted patient records

Among transplanted patients with MPS, 63% (26/41) had MPS II. The 5-year survival rate after treatment of MPS II was 88.5% during the period from 1990 to 2003. Clinical records were collected for the 21 surviving patients (81%) from eight hospitals: Type A (n = 1), Type B (n = 6), Type C (n = 7), and Type D (n = 7) [Tables 1 and 2]. Donor state, transplantation protocol, and chimeric status are also summarized in Table 2. Two patients with Type B disease (patients 10-3 and 10-5) received total body irradiation (TBI) in the transplantation protocol. The donors for patients 10-7 and 7-6 were carrier siblings: patient 10-7 showed extremely low iduronate 2-sulfatase activity (25% of normal) even though complete chimera was obtained, while iduronate 2-sulfatase activity was normal in patient 7-6. Chimeric status was determined by short tandem repeats analysis in all patients except for four patients (patients 10-7, 7-8, 7-1, and 1-1) where sex chromosome was

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.

Acknowledgments

We indebted to the patients and families of the members in The Japanese MPS Family Society for providing answers to the questionnaire. We thank Ms. Miho Tabe in SRL Clinical Laboratory Inc. for providing the data on uronic acid concentrations in HSCT-treated patients. We also thank Drs. Toru Yorifuji, Hiraku Doi, and Takeo Kato, Department of Pediatrics, Kyoto University Graduate School of Medicine, for collecting data from historic clinical records and Dr. Yukio Miki, Department of Radiology, Osaka City University Graduate School of Medicine, for expert advice on evaluating MRI lesions.

This study was supported by grant H20-Clinical Study General-011, and the matching fund subsidy of "Research on Measures for Intractable Diseases" project from the Ministry, of Health, Labour and Welfare, Japan.

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肝臓移植で治療可能になった先天代謝異常症

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はじめに

先天代謝異常症に対する肝移植の歴史は古く，Dobois らにより 1971 年に Wilson 病に対して肝移植が行われたのが最初である[1]。わが国での先天代謝異常症に対する肝移植は，京都大学で 1987 年 porphyria に対する生体肝移植が初例である。

先天代謝異常症はアミノ酸・糖質・脂質の代謝異常により，成長発達障害などをきたし，重症型では致死的となりうる代謝発作をくり返しきたす疾患群である。代謝発作は，救命できても神経学的後遺症を残すことが少なくない。内科的治療で治癒は期待できず，多くの疾患で厳密な食事療法が必須であり，患者および家族の QOL は不良で，食事療法による脂肪肝や二次的な肝線維化が生じる。近年わが国では，有機酸代謝異常症であるメチルマロン酸血症・プロピオン酸血症，および尿素サイクル異常症と肝型糖原病（Ⅰb 型）などに対し生体肝移植が施行され成果を上げているが，移植治療実態と予後は把握されておらず，適応判定基準も標準化されていない。先天代謝異常症には，代謝異常の場が肝臓に限局され生体肝移植にて治癒が期待できる疾患と全身性のものがあり，移植適応判定は種々の要件を考慮して行われるべきである。本稿では，肝移植による先天代謝異常症の治療について概説する。

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表 1 肝移植の適応疾患

1．欠損酵素を補充する目的で行われる肝移植

1）肝移植で代謝がほぼ是正される疾患
OTC 欠損症，CPS 欠損症，高シュウ酸血症Ⅰ型，家族性高コレステロール血症
Ⅰ型 Crigler-Najjar 症候群，プロテイン C 欠損症，血友病

2）肝移植で代謝が完全には是正されない可能性のある疾患
有機酸血症（メチルマロン酸血症，プロピオン酸血症）
糖原病Ⅰa 型，Ⅰb 型
シトルリン血症Ⅰ型，アルギニノコハク酸尿症

2．肝不全，肝腫瘍の治療目的に行われる肝移植
Wilson 病，シトリン欠損症（NICCD，CTLN2），チロシン血症Ⅰ型
先天性胆汁酸代謝異常症
3β-hydroxy-Δ5-C27-steroid dehydrogenase/isomerase
3-oxo-Δ4- steroid 5β-reductase
oxysterol 7α-hydroxylase deficiency
家族性進行性肝内胆汁うっ滞症（胆汁酸トランスポーターの異常）
PFIC-1（Byler 病），PFIC-2，PFIC-3
α_1アンチトリプシン欠損症，新生児ヘモクロマトーシス，ミトコンドリア呼吸鎖異常症
ガラクトース血症Ⅰ型，肝型糖原病（Ⅰa 型，Ⅰb 型，Ⅲ型，Ⅳ型，Ⅷ型）
肝型ポルフィリン症，肝嚢胞線維症

Ⅰ．わが国における先天代謝異常に対する生体肝移植の現状

1．肝移植の適応（表 1）

先天代謝異常症の肝移植の適応疾患は，「欠損している酵素を補充する目的で行われる肝移植」と「肝不全，肝腫瘍の治療目的に行われる肝移植」に分類可能である。前者はさらに移植により代謝がほぼ完全に是正される疾患と，完全には是正されない疾患に分類される[3]。

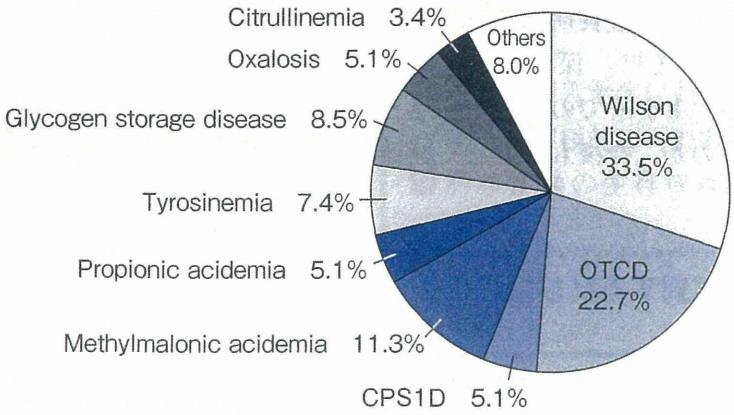

図 1　わが国における小児先天代謝疾患に対する生体肝移植（1987～2010）

2．わが国における先天代謝異常に対する生体肝移植

先天代謝異常に対する小児期の生体肝移植は1987～2010年末までに194例実施されている（図1）。銅代謝異常で肝硬変にいたるWilson病が59例（33.5%）と最多で，尿素サイクル異常症（オルニチントランスカルバミラーゼ欠損症：OTCD，カルバミルリン酸合成酵素1欠損症：CPS1D）49例（27.8%），有機酸代謝異常症（メチルマロン酸血症，プロピオン酸血症）29例（16.4%）と続く。代謝性疾患に対する生体肝移植の累積生存率は1年，5年，10年で90.0%，84.8%，82.9%と安定した成績の治療手段である[2]。Wilson病・尿素サイクル異常症・有機酸代謝異常症の累積生存率は5年，10年で87.8%，86.6%・95.2%，95.2%・85.0%，85.0%と比較的良好であるが，高シュウ酸尿症（oxalosis）は累積生存率50.4%と非常に悪い。シュウ酸沈着のため，肝移植と同時に腎移植を考慮する必要があり，単一生体ドナーからの2臓器同時摘出が倫理的に困難であること，肝移植後腎移植までの透析管理が非常に難しいことによると思われる[4]。高シュウ酸尿症1型は，診断がつきしだい肝移植を考慮すべきである。

先天代謝異常症に対する小児生体肝移植の年次別累積症例数をみると，2007年以降の尿素サイクル異常症の増加，Wilson病に対する肝移植症例数の減少が明らかである（図2）。これは，尿素サイクル異常症の長期予後が悪いと報告されてきたこと，尿素サイクル異常症に対する肝移植成績が良好であると認知されたこと，Wilson病の早期診断・治療が進歩してきたことがあげられる[5～8]。

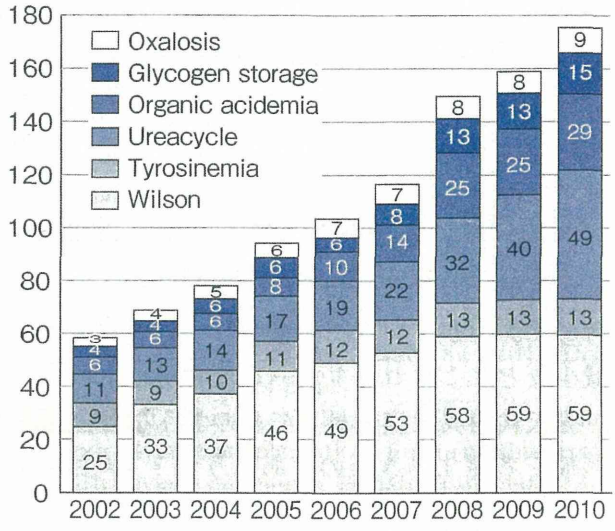

図 2　小児先天代謝疾患の累積症例数（n=194）

3．先天代謝異常症に対する生体肝移植時のドナー選択

先天代謝異常症に肝移植を考慮する場合，わが国では脳死肝移植待機順位が高位にならないため，生体ドナーで肝移植を考慮せざるをえない。生体肝移植をWilson病保因者ドナーで実施した場合，術後銅代謝異常が軽度認められるが，ドナー・レシピエントの長期経過に問題がないことが報告されている[9]。また尿素サイクル異常症においても，ドナーOTC活性が部位により大きく異なり，比較的低いことが報告されているが，ド

ナー・レシピエントともに術後長期経過で問題のないことが報告されている[10]。保因者の可能性がある両親がドナーで，ドナーでの疾患発症などの長期的な問題がないのか，今後も注意深く経過観察が必要である。

Ⅱ．先天代謝異常症に対する肝移植のスコアリング

肝移植はドナーを必要とし，ときに死亡の可能性がある治療法ではあるが，周術期管理の改善で回避できるリスクも多々ある。移植適応症例の選択に際しては，状態が良いうち（腎機能低下などがない状態）に移植をするほうが術後の成績は良好である。

移植成功例では，疾患の治癒が見込めない場合でも，QOL は明らかに改善することが多い。とくに頻回の食事療法や食事制限は，疾患により解除が可能となるものと制限を継続する必要のあるものがあるが，同じ制限をする場合でも，嘔気の減少などによりコントロールは容易となる。

先天代謝異常症に対してどのような場合に，肝移植を考慮すべきなのであろうか？ 厚生労働省の難治性疾患克服事業〔「有機酸代謝異常症（メチルマロン酸血症・プロピオン酸血症），尿素サイクル異常症（CPS1 欠損症，OTC 欠損症），肝型糖原病の新規治療法の確立と標準化に関する研究」班（代表　堀川玲子）〕で「代謝性疾患生体肝移植の手引き―適応基準」が作成された。先天代謝異常症に対する肝移植適応のスコアリングを**表 2** に示す。先の表 1 において肝移植で代謝がほぼ是正される疾患，内科治療でも頻回（年 6 回以上）の入院を必要とする場合，また代謝不全により血液浄化療法・ICU 管理を年 2 回以上要する症例などで高スコアとなる。スコアが 10 点以上で肝移植適応と判断するものである。国立成育医療研究センターでは本スコアリングシステムを用いて実際に肝移植適応・時期を判定している。

表 2　肝移植のためのスコアリング

項　目	スコア 5	3	1
疾患特異性			
代謝異常が肝臓に限局しているか？	●		
移植治療の実績があるか？		●	
内科的治療の有効性			
頻回の入院を必要とする代謝不全（年間 6 回以上）	●		
入院を必要とする代謝不全（年間 3～5 回）		●	
外来治療を必要とする代謝不全（年間 6 回以上）			●
代謝不全による血液浄化療法・ICU 入院　（初回発作時を除く，年間 2 回以上）	●		
服薬・食事療法コンプライアンス・アクセプタンス　著しく不良		●	
服薬・食事療法コンプライアンス・アクセプタンス　不良			●
QOL			
経管栄養・頻回の栄養（改善が見込める場合）		●	
神経学的改善・悪化の防止		●	
現在の状況			
神経学的状況（発達）：日常活動がある程度できる			●
身体的状況（成長）：成長障害（身長＜－2.5 SD）			●
生化学的所見：異常値の持続*		●	

* 高アンモニア血症，高乳酸血症，アシドーシス，肝機能異常，高脂血症，低血糖など

スコア　10≦適応　7≦適応を考慮する
5≦適応は慎重に考える　3＞非適応

Ⅲ．肝移植医療を考えるべき先天代謝異常症

国立成育医療研究センターでは，2005 年 11 月～2012 年 3 月までの 6 年間に 192 例の肝移植を実施してきた。現在までの患者生存率は 89.6%である。先天代謝異常症に対する肝移植は尿素サイクル異常症 13 例（OTCD 6 例，CPS1D 7 例），有機酸代謝異常症 15 例（メチルマロン酸血症 12 例，プロピオン酸血症 3 例），糖原病 9 例（1b　8 例，Ⅲa　1 例），Wilson 病 2 例，高シュウ酸尿症 2 例，familial intrahepatic cholestasis type 2　2 例，neonatal intrahepatic cholestasis caused by citrin deficiency　1 例，oxys-

terol 7α dehydroxylase deficiency　1例，ミトコンドリア呼吸鎖異常症1例の46例で，全肝移植の24.0%を占める。先天代謝異常症に対する肝移植成績は患者生存率95.7%と，他疾患と比較しても良好である。

上記疾患のなかで肝不全（非代償性肝硬変や劇症肝炎）にいたる疾患の肝移植適応に異論は少ないと思われるが，欠損酵素を補充する目的で行われる肝移植で，日常診療において肝移植の時期判断に迷う症例が多い。表1に提示した適応疾患のなかで，内科治療が奏功し臨床症状を認めない症例に，生命予後を左右する可能性のある肝移植医療を推進すべきではないと考えるが，有症状の尿素サイクル異常症，高シュウ酸血症Ⅰ型，家族性高コレステロール血症は確定診断がつきしだい，家族に将来的な肝移植医療の可能性を説明すべきであろう。また糖原病1bは，血糖コントロールが容易になり，肝移植後に免疫抑制薬を投与しているにもかかわらず易感染性が是正されるため，積極的に肝移植を考慮すべきと考えている[11]。

おわりに

肝移植医療は他者からの臓器を必要とし，ときに合併症・感染症で死亡する可能性もあるリスクの高い医療であるといわれている。100%にいたらない生存率を鑑みると，確かにリスクの高い医療だといえるかもしれない。しかし，大好きな食べ物・母親の作った食事が自由に食べられないなどの切実な子ども・家族の訴えは，95.7%の安全性と対比した場合，危険性を共有しつつ踏み込むべき有効な治療方法なのではないかと愚考している。どちらがより重いのか，日々たいへん悩みながら診療しており，まだ答えはみつかっていない。

Key Points

1. 先天代謝異常症に対する生体肝移植はわが国でも積極的に行われている。
2. 肝移植後の生存率は95.7%と良好である。
3. 移植適応判定にスコアリングが有用である。

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造血細胞移植が有効な先天代謝異常症

加藤俊一*

はじめに

ライソゾーム病などの先天代謝異常症に対する治療法として，骨髄移植が有効であることが1980年代初頭にイギリスのHobbsらによって報告されてから30年以上が経過しようとしている[1]。その間，移植細胞源が骨髄のほかに末梢血幹細胞，臍帯血幹細胞が加わり，これらの幹細胞を提供するドナーも血縁者から非血縁者に拡大されている。

一方で，1990年代中半から各種の先天代謝異常症に対する酵素補充療法が開発
おいても6つの疾患において7
可され，先天代謝異常症における
歩している。

本稿では，造血細胞移植が有効である疾患とその効果などについて概説し，酵素補充療法（enzyme replacement therapy：ERT）とどのように使い分け，あるいは組み合わせていくべきかという問題についても，最近の国際的なコンセンサスを中心に述べてみたい。

なお，「造血細胞移植」は「造血幹細胞移植」ともいわれてきたが，本稿では最近，一般的に用いられている「造血細胞移植」という用語で統一することとする。

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Ⅰ．造血細胞移植の歴史と原理

1．開発から臨床応用まで

原爆開発のマンハッタン計画の中で放射線による造血障害の治療法として研究が開始された骨髄移植は，1960年代からシアトルのThomasらにより臨床応用が始められ，1970年代には治療法の原型が確立された。1980年代以降には，造血器の悪性腫瘍である白血病や造血障害である再生不良性貧血などの血液疾患の根治療法として，積極的に実施されるようになっている。

多植の原理

球，血小板などの血球は1種類の造血幹細胞から分化することから，造血幹細胞を移植することによってこれらの血液細胞を再生することが可能となる。

1）造血幹細胞源

成体における造血幹細胞は主に骨髄の中に存在し，ごく少量が末梢循環血流中にも見出される。したがって，造血細胞移植は骨髄細胞を移植することから始まり，1980年代になり顆粒球コロニー刺激因子（granulocyte colony stimulating factor：G-CSF）により骨髄中の幹細胞を末梢血中に動員することが可能になり，移植細胞源として末梢血幹細胞が加わった。さらに1980年代後半になり，分娩直後の胎盤中に残った胎児の血液中に未分化で増殖能力に富む幹細胞の存在が明らかにされ，第3の造血幹細胞として臍帯血幹細胞が移植に用いられるようになった。

2）ドナーとレシピエントのHLA適合性

造血細胞移植においては，造血幹細胞の提供者であるドナーとその受容者であるレシピエントの

組織適合性抗原が一致していることが必要であり，ヒトにおける主要組織適合抗原は HLA (human leukocyte antigen) とよばれている。HLA はヒト 6 番染色体短腕上に数珠つなぎ状に並ぶ遺伝子群によって規定され，クラスⅠ (A, B, C) とクラスⅡ (DR, DQ, DP) の抗原がある。このうち，臨床的には A, B, C, DR の 4 座が重要と考えられている。各遺伝子座には 2 つの遺伝子があることから，レシピエントと 8 つの抗原が一致するドナーから移植が行われる。

当初，これらの抗原の同定は抗血清による抗原抗体反応により行われたことから「血清型」とよばれ，その後，遺伝子を直接同定できるようになり，「遺伝子型 (またはアリル)」としてより詳細なタイプ分けが可能になっている。

健康なドナーからの移植を「同種移植」(同じヒトという種の間で行われるという意味) といい，患者自身の造血幹細胞による移植を「自家 (自己) 移植」という。同種移植におけるドナーは HLA 一致の血縁者 (多くは同胞) が選ばれるが，血縁ドナーを見出せない場合には骨髄バンクや臍帯血バンクからの HLA 適合非血縁者ドナーを探すことになる。骨髄移植では HLA 完全一致ドナーからの移植が鉄則であるが，臍帯血移植においては 1〜2 つの HLA が不一致のドナーからの移植も可能である。

3) 前処置

移植したドナーの造血幹細胞がレシピエントの骨髄中に生着するためには，宿主側の免疫能と造血能を枯渇させなければならない。このような治療を「前処置」といい，大量の免疫抑制薬 (白血病などでは抗がん薬) の投与と放射線照射 (全身または部分的照射野) を単独もしくは組み合わせて行う。

前処置には免疫能と造血能をすべて枯渇するような「骨髄破壊的前処置 (myeloablative conditioning：MAC)」と，主に免疫能を枯渇する「骨髄非破壊的前処置 (reduced intensity conditioning：RIC)」がある

4) 移植片対宿主病とその予防

移植した造血幹細胞が生着する過程にはドナーのリンパ球による宿主を非自己と認識した免疫反応が起こり，「移植片対宿主病 (graft-versus-host disease：GVHD)」とよぶ。GVHD には移植後 1〜2 か月に起こる急性 GVHD と，3 か月以降に起こる慢性 GVHD がある。ともに重症化すれば致命的となる合併症である。

同種造血細胞移植では，計画的な GVHD 予防が不可欠で，シクロスポリン (cyclosporine：CYA)，プログラフ (tacrolimus：TAC)，メソトレキセート (methotrexate：MTX) などを組み合わせて使用する。

Ⅱ. 先天代謝異常症における造血細胞移植

1. 病変修復のメカニズム

造血系の病気である白血病や再生不良性貧血で造血細胞移植が有効であることは理解しやすいが，血液細胞には異常のない先天代謝異常症で造血細胞移植が治療効果を発揮できるメカニズムについては解説が必要であろう。

ライソゾーム病などの先天代謝異常症においては欠損する酵素は白血球などの血液細胞でも産生されることから，健康なドナーからの造血細胞移植が成立すれば，移植された血液細胞から酵素が血中に放出されて蓄積した代謝中間産物を分解することができるようになる。つまり，永続的な酵素補充が生体内で可能となる。

このような酵素産生メカニズムに加えて，移植された造血幹細胞に由来する単球・マクロファージ系の細胞が各種組織内で分化し，肺では肺胞マクロファージ，肝臓ではクッパー細胞や伊東細胞，腹腔内では腹腔マクロファージ，皮膚ではランゲルハンス細胞，脳ではミクログリアやアストロサイト，骨では破骨細胞などに分化し，直接組織内で代謝を営むことが期待される (図 1)。

補充した酵素や血球で産生された酵素が血管脳関門 (blood brain barrier：BBB) を通過することができないのに対して，造血細胞移植で産生されたドナー幹細胞に由来する単球が BBB を通過して microglia となっていることや，脳内病変の修復を行っていることが種々の事実により明らかにされている。

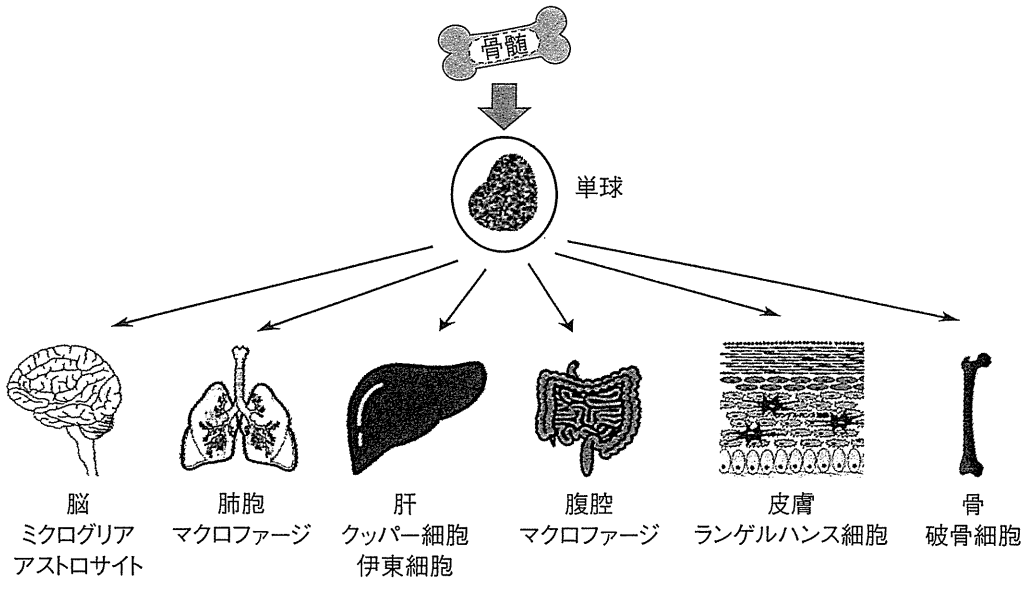

図 1　移植した骨髄から産生される単球から組織マクロファージへの分化

2．先天代謝異常症における造血細胞移植の問題点

1）ドナー

家族内のドナーの場合には同一疾患の保因者であることがあり，酵素活性が健常者の半分程度に止まる可能性がある。最近では，血縁保因者よりも酵素活性が正常な非血縁者ドナー（骨髄もしくは臍帯血）を優先すべきではないかという意見が多い。

2）前処置

先天代謝異常症においては患者の免疫能は正常であることから，MAC で前処置を行っても生着不全（拒絶）になることが白血病などにおける移植よりも多い。また，先天代謝異常症は非腫瘍性疾患であることから放射線照射は極力さけるべきであることから，ブスルファン（busulfan：BU）とエンドキサンを主体とした前処置が多用されてきた。しかし，乳幼児では BU による肝中心静脈閉塞症などの合併症が問題となることから，最近では BU の代わりにフルダラビンや treosulfan を用いた前処置が試みられている[2]。

なお，副腎白質ジストロフィー（adrenoleukodystrophy：X-ALD）では BU 投与により神経症状が悪化することがあるため，BU を含まない前処置を選択すべきである。

Ⅲ．造血細胞移植が有効な先天代謝異常症

先天代謝異常症は希少疾患であるために造血細胞移植症例が少ないことから，疾患ごとの有効性についての評価が困難であることが多い。そのため，国際的な共同研究や会議をくり返しながら造血細胞移植の適応や有効性に関するコンセンサス形成が行われてきた。

表は，ヨーロッパとアメリカの代表的な研究者たちによって先天代謝異常症に対する造血細胞移植の適応と酵素補充療法との関連についての考え方がまとめられたものである[3]。

1．ムコ多糖症（mucopolysaccharidosis：MPS）

1）Hurler 病（IH 型）

MPS の中で最も発症と進行が早く予後不良な病型であるため，造血細胞移植が絶対的適応となる。Hobbs らの最初の報告以来 500 例をこえる同種造血細胞移植が実施されており，生命予後の改善のみならず気道閉塞症状，肝脾腫，心血管系異常，難聴，視力障害，成長障害などの身体症状の改善が認められ，病初期に移植を実施しえた症例では高次認知機能や精神運動機能などの中枢神経症状の改善が得られている[4]。これらの症状の改善の程度は症例ごとに大きな開きがあり，移植

表　造血細胞移植が適応となる先天性代謝異常疾患

疾患名	欠損酵素	適応	備　考
ムコ多糖症			
Hurler（IH）	α-L-iduronidase	◎	
Hurler/Scheie（IH/S）	α-L-iduronidase	○	ERT が最初の治療
Scheie（IS）	iduronate-2-sulfatase	○	ERT が最初の治療
Hunter 重症型（II A）	iduronate-2-sulfatase	△	病初期のみ
Hunter 軽症型（II B）	iduronate-2-sulfatase	△	病初期のみ
Sanfilippo A（III A）	heparan-*N*-sulfatase	△	病初期のみ
Sanfilippo B（III B）	*N*-acetylglucosaminidase	△	病初期のみ
Sanfilippo C（III C）	acetylCoA-*N*-acetyltransferase	△	病初期のみ
Sanfilippo D（III D）	*N*-acetylglucosamine 6-sulfatase	△	病初期のみ
Morquio（IV）		?	
Maroteaux-Lamy（VI）	arylsulfatase B	○	ERT が最初の治療
Sly（VII）	β-glucuronidase	○	
白質ジストロフィー			
X-ALD，大脳型	ALD 蛋白	◎	進行例は適応外
MLD，早期発症型	ARSA	?	病初期のみ
MLD，遅発型	ARSA	◎	
GLD，早期発症型	GALC	◎	進行例は適応外
GLD，遅発型	GALC	○	
糖タンパク代謝異常等			
fucosidosis	fucosidase	○	
α-mannosidosis	α-mannosidase	○	
aspartylglucosaminuria	aspartylglucosaminidase	?	
Farber	ceraminidase	?	
Tay-Sachs，早期発症型	hexosaminidase A	?	病初期のみ
Tay-Sachs，若年型	hexosaminidase A	?	
Sandhoff，早期発症型	hexosaminidase A & B	?	病初期のみ
Sandhoff，若年型	hexosaminidase A & B	?	
Gaucher 病 I（成人型）	glucoserebrosidase Glucoserebrosidase	○	ERT が最初の治療
Gaucher 病 II（乳児型）	glucoserebrosidase Glucoserebrosidase	?	
Gaucher 病 III（若年型）	glucosidase	?	ERT の効果限定的
Gaucher 病 III（Norrbottnian）	acid sphingomyelidase	○	
Pompe	acid sphingomyelidase	△	ERT 実施可能
Niemann-Pick：type A	cholesterole trafficking	?	
Niemann-Pick：type B	*N*-acetylglucosamine-1-phosphotransferase	?	ERT 治験中
Niemann-Pick：type C	acid lipase	○	
Mucolipidosis II（I-cell）	sulfatases	△	病初期のみ
Wolman syndrome		○	標準治療に近い
MSD		○	

◎：標準治療　○：症例により適応　△：実験的　？：不明　（Boelens ら[3] 2010 より一部改変）
ERT：酵素補充療法

時の年齢が若いほど（2 歳未満），移植時の神経障害が軽いほど（DQ＞70）移植による改善度が高いことが多くの報告で確認されている。

ドナーの酵素活性レベルと移植の結果の間の相関の有無については，肯定する報告と否定的な報告があった。最近の国際共同研究により，ドナーの酵素活性が高いほど移植後の症状の改善が良好であるとの結論が得られている[5]。

過去 30 年間の欧米における無イベント生存率（ドナー細胞の生着が得られたうえでの生存率）を 2004 年までの期間と 2005 年以降の期間で比較したところ，53%から 91%に向上していた（図 2）[3]。2004 年までは施設別に異なった移植プロトコールが用いられていたが，2005 年から EBMT（European Blood and Marrow Transplant Group）標準プロトコールが導入されたことによって生着不全や混合キメラが減少した。また，移植細胞源として非血縁の臍帯血幹細胞を用いる

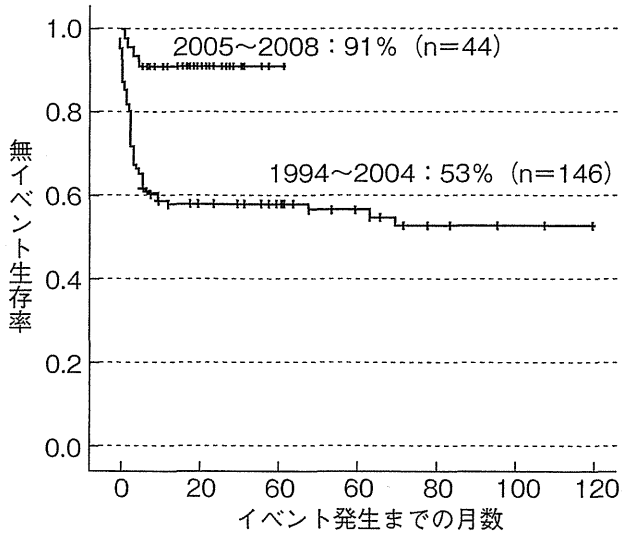

図 2　Hurler 病における造血細胞移植後の無イベント生存率（ドナー細胞が生着したうえでの生存率）の年代的比較
（Boelens ら[3] 2010 より一部改変）

ことにより，迅速な移植が可能になったことも大きな要因となったとされている。

2000 年代前半に臨床応用された ERT により身体症状の改善は得られるようになったものの，投与された酵素が BBB を通過しないため，重篤な神経症状には効果が期待できないことが判明し，MPS-IH ではドナーが得られしだい造血細胞移植を実施することが国際的なコンセンサスとなっている。ERT は移植実施までの期間の身体症状改善には有用であり，一部の症例では酵素を直接髄注することなども試みられている。

このように，造血細胞移植と ERT という 2 つの治療法が選択可能となると，どのような症例にどのような時期にどのような治療を行うべきかについてガイドラインが必要となり，ヨーロッパコンセンサス会議からは，以下のような結論が発表されている[6]。

①2 歳 6 か月までに診断された Hurler 病（MPS-IH）と診断された症例では造血細胞移植が推奨治療となる。

②MPS I 型でも神経症状が軽いかほとんどない Hurler/Sheie（IH/S）や Sheie（IS）においては，症例ごとに重症度やドナーの存在などにより造血細胞移植の適応を検討すべきである。

③すべての MPS I 型症例は移植の既往の有無にかかわらず ERT を行うメリットがある。

④ERT は診断が確定しだい開始すべきであり，造血細胞移植までの準備期間に実施しておくことが望ましい。

2）Hunter 病（II 型）

日本人などアジア地域においては MPS の中ではII型の Hunter 病が最も頻度が高い病型であり，X 連鎖劣性の遺伝形式のため男児にのみ発症する。Hurler 病に較べ発症が遅く，表現型も中枢神経症状を伴う重症型から伴わない軽症型まで幅広い。

欧米における造血細胞移植の成績は一定せず，Krivit らは否定的な見解を示していたが，最近発症早期に移植を実施しえた症例では効果を期待できるとする報告が出ている[7]。わが国では症例数も多いことから Hunter 病における造血細胞移植は多く実施され，睡眠時無呼吸などの呼吸器症状，関節拘縮，皮膚硬化，肝脾腫などの身体症状は著しく改善し，心臓の弁膜障害についても進行が停止するなどの効果が確認されている。しかし，神経症状を伴う重症型では MRI 上のムコ多糖蓄積所見の改善や水頭症への進行停止などの効果が認められるが，認知能力の明確な改善効果は乏しい。

Hurler 病における造血細胞移植による中枢神経症状への効果と較べて Hunter 病では明確な効果が認められていない理由として，Hunter 病での移植のほとんどが 2 歳以降に実施されていることから，中枢神経系の病変が不可逆的になっているためではないかとの考えが有力である。そのため，最近ではできるかぎり早く移植を実施することにより症状の進行を停止するという目的で，Hurler 病と同様に診断が確定ししだい臍帯血移植などを行うことも試みられている[8]。

3）その他の MPS

その他の MPS の病型で造血細胞移植の有効性が証明されているのはVI型の Maroteaux-Lamy 病とVII型の Sly 病である。とくにVI型の多くは知能障害を伴っていないので，病初期に移植を行えば高い臨床効果を期待できる。

III型の Sanfilippo 病では A～D のいずれの亜