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Long-term therapeutic efficacy of allogenic bone marrow transplantation in a patient with mucopolysaccharidosis IVA☆

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ABSTRACT

Mucopolysaccharidosis IVA (MPS IVA) is one of the lysosomal storage diseases. It is caused by the deficiency of N-acetylgalactosamine-6-sulfate sulfatase. Deficiency of this enzyme leads to accumulation of the specific glycosaminoglycans keratan sulfate and chondroitin-6-sulfate. This accumulation has a direct impact on cartilage and bone development, resulting in systemic skeletal dysplasia. There is no curative therapy for this skeletal dysplasia.

This report describes long-term therapeutic efficacy in a 15-year-old boy with a severe form of MPS IVA who received successful allogeneic bone marrow transplantation (BMT) from his HLA-identical carrier sister. The level of the GALNS enzyme in the recipient's lymphocytes reached almost half of normal level within two years after BMT. For the successive 9+ years post-BMT, GALNS activity in his lymphocytes maintained the same level as the donor's, and the level of urinary uronic acid was reduced. Lumbar bone mineral density increased around 50% one year later post-BMT and was kept consistent. Radiographs showed that the figures of trochanter major and minor appeared, while the epiphyseal dysplasia in the femoral cap was almost unchanged. Loud snoring and

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apnea disappeared. Vital capacity increased to around 20% for the first two years and was maintained. Activity of daily life (ADL) was improved in work/study efficacy, respiratory status, sleep, joint pain, and frequency of infection.

In conclusion, the long-term study of hematopoetic stem cell transplantation has shown clinical improvements in respiratory function, radiograph findings, ADL, and biochemical findings, suggesting that it is a potential therapeutic option for patients with MPS IVA.

1. Introduction

Mucopolysaccharidosis IVA (MPS IVA; Morquio A disease) (OMIM #253000) is an autosomal recessive lysosomal storage disorder that is caused by defective N-acetylgalactosamine-6-sulfate sulfatase (GALNS). GALNS deficiency leads to accumulation of keratan sulfate (KS) and chondroitin-6-sulfate in lysosomes and excessive urinary excretion of these substrates [1].

Patients with MPS IVA have a wide spectrum of clinical manifestations [1–7]. Patients with MPS IVA appear healthy at birth. Major signs and symptoms in most patients are usually observed before their first birthday, including kyphosis, protrusion of the chest, and prominent forehead [8]. Milestones for walking are often delayed. Patients with MPS IVA are usually evaluated during the second year of life for unique skeletal features including knock-knee, growth retardation, laxity of joints, and abnormal gait with a tendency to fall in addition to kyphosis, protrusion of the chest, and prominent forehead. Patients with MPS IVA can usually be distinguished clinically from patients with other MPS by preservation of intelligence and characteristic skeletal changes manifesting as a spondyloepiphyseal dysplasia with unique laxity of joints (knee, hand cervical spine, hip) and cervical instability. Odontoid hypoplasia is the most critical skeletal feature to be found in most patients. Odontoid hypoplasia in combination with ligamentous laxity and extradural GAG deposition can result in atlantoaxial subluxation and/or cervical stenosis with or without cord compression, cervical myelopathy or even death [2–7].

Other potential complications include airway and pulmonary compromise, muscle weakness, heart valvular disease, hearing loss, fine corneal clouding, and widely spaced teeth with abnormally thin enamel. Patients with a severe phenotype often do not survive beyond the second or third decade of life, primarily related to cervical instability and pulmonary compromise. Most patients have difficulty with anesthesia due to a narrow airway and a small, restrictive lung. Difficulty with both upper and lower airways increase as the disease progresses and greatly increases the risk of anesthesia and sedation [9]. Patients with mild manifestations of Morquio A have been reported to survive into the seventh decade of life [2–6].

Therapies for MPS have been developed for the last two decades experimentally and clinically. These include enzyme replacement therapy (ERT), gene therapy, and hematopoietic stem cell transplantation (HSCT), leading to the partial improvement of clinical phenotypes. ERT is approved for use in patients with mucopolysaccharidosis I (MPS I) [10], MPS II [11,12], and MPS VI [13–16]. A clinical trial for MPS IVA has been conducted. Patients treated with ERT showed clinical improvement of somatic manifestations and improved quality of life. However, there are several limitations with current ERT: i) limited effect on neurological and skeletal symptoms [17,18], ii) rapid clearance from the circulation, and iii) immunological issues (antibody production leads to reduced efficacy) [10,19–21]. Experimental gene therapies have been tested in animal models and human subjects [22,23]. However, viral vectors for gene therapy have not been delivered to bone efficiently, and targeting the viral vector to bone remains a major challenge [4,5,24].

HSCT has been proposed as a treatment for inherited lysosomal storage diseases to correct other cells, which take up enzyme secreted by the bone marrow-derived cells. Bone marrow transplantation (BMT) has been performed on Hurler syndrome (MPS IH) patients, resulting in clinical improvement of somatic manifestations and cognitive function if it is completed before age 2 years [25,26]. Tanaka et al. [27] have

Fig. 1. X-ray and MRI photographs with age. Lateral view of thoracolumbar vertebra (a, b, c), neck (d), a front view of femoral region (e, f, g), pre-BMT (a, e, h), three years later post-BMT (b, f), and nine years later post-BMT (c, g, i). Platyspondylia and anterior beaking of thoracolumbar vertebra increased slightly in size and the margin of vertebra became clear (a, b). Deformity of capital femoral epiphysis was almost unchanged, but trochanter major and minor obviously appeared (f, g).

addressed that HSCT in patients with MPS II provides a positive effect in cognitive function when HSCT is conducted before signs of brain atrophy and that HSCT is one of the options in an early stage of the disease [27]. HSCT also shows some benefits in physical activity. Thus, HSCT in patients with MPS improves quality of life, but the therapeutic effect remains unknown in bone lesions [28].

To date, there has been no detailed report of the systemic clinical consequence for HSCT in patients with MPS IVA [4,5,29,30].

In this report, we first describe the biochemical and clinical findings for 9+ years after successful allogeneic BMT in a male patient with MPS IVA.

2. Subject and clinical course

2.1. Clinical course (pre-BMT)

The patient was the fourth child born to unrelated healthy parents. No family histories of congenital anomalies and mental deficiency as well as no medications during the pregnancy were noted. The pregnancy and delivery at 40 weeks of gestation were uneventful. Compared with the age-matched control group in the Japanese population, the birth length and weight were 54.5 cm (+2.5 SD) and 3780 g (+1.0 SD), and the occipitofrontal circumference was 35 cm (+1.2 SD). At 1 year and 6 months of age, the patient had short neck, prominent chest, short trunk, genu valgum, kyphosis, and hypermobile joints of fingers and wrist with the suspicion of congenital spondyloepiphyseal dysplasia. At 5 years and 3 months of age, he developed waddling gait with prominent knock-knees, but maintained normal intelligence (Supplementary Fig. 1a). His height and weight were 90 cm (−3.9 SD) and 14.5 kg (−1.3 SD), respectively, compared with the age-matched control group. His Kaup Index (BMI) [body weight $(kg)/height (cm)^2$] was 17.9 (overweight; >17.0) (Supplementary Fig. 2). When compared with the age-matched male patients with MPS IVA, his height and weight were below 25th percentile and BMI was at 75th percentile. At 8 years of age (Supplementary Fig. 1b), the patient had walking difficulty complicated by atlanto-axial subluxation with odontoid dysplasia and underwent the operation of atlanto-axial fixation. At 9 years of age, he suffered from glaucoma and foveation of optic disk. At 14 years of age, the patient was referred to University of the Ryukyus for chest pain and was diagnosed as MPS IVA by enzyme assay of GALNS. Imaging study presented platyspondylia and anterior beaking of thoracolumbar vertebra (Fig. 1a), stenosis of spinal canal (Fig. 1d), deformity of acetabulum and capital femoral epiphysis (Fig. 1e), ulnar deviation (Fig. 1h), and a trace of tricuspid insufficiency. No mutation was found in all the 14 exons and each exon–intron boundary region in the GALNS gene. Cervical myelopathy by stenosis of spinal canal brought on muscle weakness. The patient underwent cervical decompression/fusion surgery, resulting in disappearance of surgical myelopathy. He could not assume a half-sitting posture, squeeze a towel, or sit without support. He had orthopnea all night, loud snoring, postural dyspnea, occasional shortness of breath, and required a wheelchair for movement (Supplementary Fig. 1c). His anus was beyond his reach for his short arms. He had mild corneal clouding and glaucoma under medication. He had neither hepatosplenomegaly nor hearing impairment.

The study protocol was in accordance with the standards of the Ethics Committee in the Ryukyus Graduate School of Medicine (Okinawa, Japan).

No mutation was found, although DNA analysis was performed. Further detailed investigation should be required.

2.2. BMT procedure

At 15 years and 8 months of age, BMT with marrow from an HLA-identical elder sister was performed. The patient's height and weight were height 103 cm (−11.2 SD) and 40.7 kg (−1.8 SD), respectively. His Rohrer index [body weight $(kg)/height (cm)3 \times 10^7$] was 372 (obese; >160) and BMI was 38.4, compared with the age-matched Japanese control group (Supplementary Fig. 2). His height and weight were above 75 percentile and below 25th percentile of the patients with MPS IVA, respectively, while BMI was at 97th percentile. Conditioning consisted of busulfan (4 mg/kg/day × 4 days), cyclophosphamide (50 mg/kg/day × 4 days), and anti T-lymphocytic globulin (15 mg/kg/day × 4 days). After BMT, cyclosporine (1.5 mg/kg × 2 div/day × 30 days intravenously and successive oral administration for 100 days) and

Table 1

The pre- and post-transplant biochemical and physiological data.

Age (years, months)	9y and 3m	13y and 10m	15y and 7m	15y and 8m	16y and 5m	17y and 9m	18y and 11m	19y and 4m	19y and 11m	21y and 3m	22y and 1m	23y and 0m	24y and 1m	24y and 11m
GALNS (nmol/mg protein/17h)		2.8				73.6	92.8		140	126	140		131	124
Urine uronic acid (mg/dl cre)		27	36.4	B	42.5	23.6	19.1		20.6	25.9	20		23	7.8
Urine keratan sulfate (%)		9	3	M	3	7	0		6	3	4		7	0
Lumber BMD at L2–4 (g/cm2)	0.318		0.372	T	0.548	0.442	0.539	0.463	0.575	0.475	0.414	0.440	0.447	0.456
%Age matched mean of BMD (%)	48.9		39.6		55.6	43.1	51.3	43.7	54.2	44.4	38.7	41.1*	41.8*	42.6*
VC (L)			1.08		1.14	1.31	1.31		1.32	1.38	1.37	1.34	1.28	1.34
%VC (%)			43		43.2	48.7	48.2		50.0	52.5	52.5	51.1	49.6	51.7
FEV1.0 (L)			1.08		1.01	1.29	1.12		1.2	1.16	1.19	1.16	1.13	1.12
%FEV1.0 (%)			52.7		47.7	61.9	54.6		62.6	63.1	63.8	62.6	63.3	64.0
PEF (L/s)			2.03		2.67	2.32	2.38		2.16	2.09	2.36	2.19	1.91	2.42
%PEF (%)			35.6		45.7	39.8	41.0		38.3	37.8	42	37.8	34.7	44.1

GALNS (normal range:187–330); urine uronic acid (normal range: n = 8, 10.3 ± 2.3); *, a percentage of the mean BMD of 22 years of age (1.07 g/cm^2).

methotrexate (7–10 mg/day × 3/one week) were given. Fluorescent in-site hybridization (FISH) chromosomal analysis showed that a 46,XX cell was presented in 99% of 500 bone marrow cells in 42 days after BMT. He was discharged from the hospital 62 days after transplantation. On day 60, his minor red blood cell antigens were found to be completely donor type. No graft-versus-host disease was observed.

2.3. Clinical course (post-BMT)

Analyses of urinary uronic acid and enzyme assay of GALNS were measured by SRL Inc. (Tokyo, Japan). Two years after BMT, the enzyme activity of GALNS in white blood cells increased from 2.8 to 73.6 (nmol/mg protein/17 h, normal range; 187–330) and was maintained at the almost half of normal level as observed in his carrier donor sister (Table 1). In his spot urine test, the level of uronic acid decreased around 35% from pre-BMT (15 years and 7 months) to post BMT (17 years and 9 months) and was maintained at the same level during the following period. At 24 years and 11 months of age, the latest level of uronic acid was reduced to 21% of pre-BMT level (7.8 mg/dl cre). Urinary KS consistently occupied 0–9% of total urinary GAGs over the period before and after BMT. CHESTC 55 V (CHEST Corp.) before 19 years of age and CHESTAC9800 (CHEST Corp.) after 20 years of age was used for spirometry to evaluate pulmonary function. Three years post BMT, vital capacity (VC) increased from 1.08 to 1.31 (L), %VC from 43 to 48.2 (%), peak expiratory flow (PEF) from 2.03 to 2.36 (L/s), and one second forced expiratory volume ($FEV_{1.0}$) increased from 1.08 to 1.12 (L), although his height was unchanged at 106 cm. During 9 + years post-BMT, the level of the pulmonary function was stabilized.

EXP5000 (Lunar, GE Healthcare) was used to measure bone mineral density (BMD) of the lumbar spine by dual-energy X-ray absorptiometry (DXA). We used the data of normal BMD values for L2–L4 published for Japanese healthy children [31]. One year later post-BMT, BMD at L2–4 increased from 0.372 to 0.548 (g/cm^2) and was maintained at the level of 0.48 ± 0.054 for the following 9 years. Radiographs showed that platyspondylia and anterior beaking of thoracolumbar vertebra increased slightly in size, while the margin of vertebra became clear (Fig. 1b,c). Three years later post-BMT, deformity of capital femoral epiphysis was almost unchanged, but trochanter major and minor obviously appeared (Fig. 1f). Nine years later post-BMT, these figures including the upper limbs remained steady (Fig. 1c,g,i). Orthopnea, loud snoring, and postural dyspnea disappeared with feasibility of breath. The patient had glaucoma status checked five years later post-BMT, and the intraocular pressure was reduced from 22 to 12 (mm Hg) (nomal range: 10–21 mm Hg) under the same medication of carteolol. Faint corneal clouding had been unchanged. Annual echocardiography showed no valvular involvement.

Thirteen months later post-BMT, the patient underwent osteotomies of both femurs without any complication of surgical and anesthesia procedures. After correction osteotomies for knock-knee, the patient could walk for 100 m by ankle–foot orthoses (Supplementary Fig. 1e,f) and for 400 m by hip–knee–ankle–foot orthoses, although after walking a long distance, the patient had pain at the ankles. To prevent the risk of dislocation of the hip, he was recommended to walk indoors within 20 m by ankle–foot orthoses and to move outdoors by electric wheelchair. Hypermobility of joints (Supplementary Fig. 1d) was unchanged for 9 + years post-BMT. At 25 years of age, he worked as a designer of computer graphics. His height and weight were 103 cm and 34 kg, respectively and his BMI [body weight (kg)/height (cm)^2] was 32.0 (obese; >30), compared with the level of the Japanese control group (Supplementary Fig. 2). His height and weight were below 25th percentile and 50th percentile of the age-matched patients with MPS IVA, and BMI was above 75th percentile. His grip strength was 3.5 kg by the right hand and 3.2 kg by the left hand (47.54 kg on the average of the age-matched Japanese male controls).

Laboratory findings showed that liver and kidney function were normal and that inflammatory factors (C-reactive protein — CRP, serum amyloid A protein — SAA, matrix metalloproteinase-3 — MMP-3) were within normal limits.

2.4. Activity of daily life

To address quality of activity of daily life (ADL) in patients with MPS objectively, we developed the ADL questionnaire with a scoring system. The questionnaire consisted of the four main sections; 1) movement (walking, stairs, hand movement, endurance), 2) movement accompanied by cognitive performance

(toileting, changing clothes, bathing, eating), 3) cognitive performance (understanding, conversation, social participation, problem solving), and 4) other symptoms (work/study, behavioral problems, sleep, pain, joint motion, respiratory status, infection, vision, hearing, skin, hair, appetite) and provided scores from 0 to 5 (0 = disabled, 5 = healthy).

The patient scored a 34 in the first three sections at pre-BMT, while he scored a 37 at 9 + years later post-BMT (the age-matched healthy control group: 60, n = 10). The patient scored a 40 in the fourth section at pre-BMT, while the score of ADL improved to 49 at post-BMT (the healthy control group: 56, n = 10). The improvement of the score was observed in activity at work/study, sleep, joint pain, respiratory status, and infection, indicating that BMT provides a better quality of daily life for a long-term follow-up.

3. Discussion

The aim of this study was to evaluate clinical and biochemical effects by BMT in a patient with MPS IVA for a long-term period and to assess further feasibility of BMT on this systemic skeletal disorder. We have demonstrated 1) the first full description of a successful BMT case with MPS IVA without a major GVHD and/or adverse effect and 2) clinical improvement in lung function, radiograph findings, biochemical findings, ADL, and ocular manifestations. These findings suggest that HSCT is a potential therapeutic option for patients with MPS IVA.

Patients with MPS IVA often require surgical interventions such as cervical fusion, decompression of spinal cord, osteotomy, and hip replacement through their lifetime. Supportive therapies (anti-inflammatory drugs) and rehabilitation provide a limited effect for bone and joints. Thus, establishment of therapy for MPS IVA remains an unmet challenge.

ERT as a potential treatment has been investigated, since it is an established and approved strategy of treating MPS including MPS I, MPS II, and MPS VI. The success of ERT largely depends upon biodistribution of the infused enzyme, which can easily reach visceral organs such as liver and spleen, but it cannot easily access cartilage and ligament secondary to their avascular region and the difficulty in distribution to the extracellular matrix (ECM) in connective tissue. Clinical trials with ERT in MPS I, II, and VI show limited improvement in joint pain, stiffness, or joint range of motion. Skeletal dysplasia is irreversible by conventional ERT, since there is little or no evidence that the current ERT directly delivers the enzyme to cartilage and bone lesions in patients with MPS. A clinical trial for MPS IVA is in progress. It is unlikely that the positive effect of ERT is due to the direct delivery of the enzyme to the cartilage. After six months of preclinical ERT in MPS IVA mice, there was little impact on bone pathology [32]. Recent surgical remnant from a 17-year-old patient in an extension clinical trial for 3 months did not show any reduction of vacuoles in chondrocytes (unpublished data). The underlying problems associated with progressive skeletal deformity and laxity of joints will not be solved by current ERT with native enzyme [5]. It may require a targeting system to enhance clinical efficacy by ERT in bone [6].

HSCT including allogeneic BMT is an alternative option for MPS and has been used to treat patients for the last two decades. BMT in the indexed patient with a severe phenotype of MPS IVA was performed in expectation of no regression of skeletal abnormalities and improvement of obstructive airway, since timing of BMT at 15 years and 8 months of age was too late to reverse the most clinical manifestations. For 9 + years post-BMT, GALNS activity in the lymphocytes of the patient maintained half the normal level reflected by the carrier donor. His clinical course improved over pre-BMT status in the disappearance of orthopnea and loud snoring. Achievement of walking was mainly supported by surgical interventions (osteotomy for knock-knee) post-BMT and was maintained in a stable condition. Surgical and anesthesia procedures were conducted without any complication including airway administration. Significant risks, including death [33,34], are associated with administering anesthesia to patients with MPS IVA. Patients become difficult to intubate and extubate before and after surgical procedures. Airway abnormalities including tortuous appearance of the trachea and bronchi were found as a result of the abnormalities in the hyaline cartilage and deposits of GAGs [9]. BMT could provide a positive impact to broaden the airway consistent with feasibility of anesthesia in the present case.

Results of BMT in the patient with MPS IVA has also shown that BMDs of spine, humerus, and femur were increased and maintained in spite of the advanced stage and that no further progression of the skeletal abnormalities developed. Trochanter major and minor in femur obviously appeared. To confirm

impact to BMD by BMT, what is required is an age-dependent BMD chart from natural course of untreated MPS IVA cases. The effect of BMT on the skeletal manifestations in this type of patient has been difficult to assess both qualitatively and quantitatively, since the bone deformity has been advanced by the age of 15 years.

Summary data of the International Morquio Registry showed that 70% of patients with MPS IVA become wheelchair-bound in the teenage years, as did the present case [2]. Based upon the registry data, we predicted that his symptoms would worsen year by year with progressive motor and respiratory dysfunctions. Respiratory failure is one of the most important causes of morbidity and mortality in patients with MPS IVA [2].

Respiratory function was improved, while progression of skeletal dysplasia was prevented. After bilateral osteotomies post-BMT, the patient became ambulatory.

In a 20-year-old male autopsied case with MPS IVA who died of respiratory failure post-cervical fusion, pathohistological analysis demonstrated storage materials in chondrocytes and multiple organs as existence of foam cells and macrophages in lung, aorta, heart valves, heart muscle, trachea, visceral organs, and bone marrow [34]. These results suggested that systemic storage materials might affect the function of multiple critical organs over a lifetime. Zustin hypothesized the delay in the regression of cartilage canals due to a local accumulation of degradation product-laden macrophages affects the regulation of epiphyseal cartilage maturing with subsequent characteristic skeletal deformities [37]. To verify the hypothesis, it will be required to test the pathological effects by BMT to foam cells and macrophages in bone marrow, chondrocytes, and other tissues once the biopsy samples are available.

The clinical outcomes of HSCT in patients with MPS have varied considerably. Factors that affect the outcome of HSCT consist of the type of the MPS disorder, the genotype and HLA typing of the donor, the degree of clinical involvement, preparative regimen and complications by HSCT, and the age at the time of transplantation [38]. Treatments of HSCT are effective, as for MPS I [25,26] and MPS II [27,39], to prevent deterioration of CNS if HSCT is conducted at an early stage. Cases of Maroteaux–Lamy syndrome (MPS VI) [40] and MPS VII [41] have been also reported with improvements of visceral organs. These types of MPS are thought to be clinically impacted by HSCT. Meanwhile, there has been no publication in patients with MPS IVA that describes the detailed clinical consequence until now [4,5,42,43]. When compared with ERT, the advantages of HSCT are 1) that it will be a one-time permanent treatment if fully engrafted, 2) that the enzyme can be supplied and circulated at the same level as the donor's level for the lifetime continuously, and 3) that the enzyme expressed in bone marrow will access the targeting site, bone, and cartilage readily. It has been thought that the HSCT procedure provides a high mortality rate in patients with MPS and that patient condition and type of disease should be carefully selected. Until now, we have seen 6 HSCT cases with a severe form of MPS IVA in Japan (age range: 5–15 years old), and 5 cases had a full engraftment successfully done (unpublished data, personal communication with Dr. Yabe at Tokai University and Dr. Tanaka at Osaka City University). No serious adverse effects/damage or death in 6 HSCT-conducted cases have been reported during the procedure. With the improved protocol, and with consideration about the selection and condition of the patient and the type of donor, the risk of HSCT could be minimized.

The overgrowth of the patient with MPS IVA was observed at birth, and his birth length was the same as + 2.5 SD of the mean birth length in the Japanese control group. It is of great interest that overgrowth in early life has been observed widely in MPS I, II, and VI as well as MPS IVA [3,6,35,36]. The cause of this initial overgrowth in patients with MPS remains unclear. It is likely that some common mechanism such as hormonal change may affect the growth during fetal development and/or during the early life of patients with MPS. The pattern of growth of patients with MPS IVA is characterized by impaired growth velocity by the first year of age that later progresses throughout life. Growth stops in patients with MPS IVA up to 5–8 years of age, as observed in the patient with a severe phenotype here. Therefore, this explains why no growth impact is provided for the present case, despite improvement of BMD, since BMT was conducted at the age of 15 years.

As with height, the birth body weight in patients with MPS IVA is above that in the normal controls and then falls below that of age-matched controls with age [3], as seen in the current patient. After 5 years of age until present, the BMI (or Kaup index, Rohrer index) in this patient was consistently above the mean value for the age-matched control and patients with MPS IVA, suggesting the patient was "overweight or obese". Therefore, one can speculate the effect of overweight or obesity on overloading the lower

extremities and the ADL in this patient. Physicians should be mindful of maintaining proportional stature in patients with MPS IVA.

Some limitations have to be considered to evaluate this BMT case precisely: 1) it is difficult to evaluate therapeutic efficacy because of the wide spectrum of the severity and the course of progression and effect of BMT in this case may not be applied to other cases; 2) we cannot directly compare the difference between treated and untreated clinical statuses in the same patient. Therefore, we have to accumulate the medical records of the patients retrospectively as well as prospectively who received BMT/CBT or ERT, and have to compare the prognosis among these patients.

In conclusion, results of successful BMT in the patient with MPS IVA indicate that no further clinical deterioration and a better quality of life could be expected in long term post-transplantation and that HSCT should not be excluded as a therapeutic option for patients with MPS IVA. Although we cannot conclude whether HSCT under the current regime is effective in other patients, long-term evaluation of patients like the current case and accumulation of data from additional patients receiving HSCT should clarify this issue. We also expect that if HSCT is performed for younger patients, skeletal abnormalities obstructive airway, and development of growth will be improved.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ymgmr.2013.11.002.

Compliance with ethics

The study protocol (reception number: H23.1–7) was in accordance with the standards of the Ethics Committee in the Ryukyus Graduate School of Medicine (Okinawa, Japan).

Informed consent

Informed consent included in this article for human subject was taken by Dr. Yasutsugu Chinen.

Animal rights

Not applicable.

Contributions to the project

Yasutsugu Chinen: He is a Principal Investigator of this project and has contributed to the concept, planning of BMT, analysis of data, and reporting of the work described in the article. He and his team conducted BMT and followed up the patient.

Takeshi Higa: He has contributed to the planning, performance of BMT, data analysis, and reporting of the work described in the article.

Yasuyuki Suzuki: He has contributed to the scoring system of activity of daily life, data analysis, and reporting of the work described in the article.

Tadao Orii: He has contributed to the planning, data analysis, and reporting of the work described in the article.

Shunji Tomatsu: He has contributed to the planning, data analysis, and reporting of the work described in the article.

Nobuyuki Hyakuna: He has contributed to the planning, performance of BMT, data analysis, and reporting of the work described in the article.

Conflict of interest

All the authors contributed to the Original Article and have no conflict of interest with any other party. Yasutsugu Chinen, Takeshi Higa, Yasuyuki Suzuki, Tadao Orii, Shunji Tomatsu, and Nobuyuki Hyakuna declare that they have no conflict of interests.

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