Long-term follow-up of a girl with Maroteaux-Lamy syndrome after bone marrow transplantation

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Background: **Mucopolysaccharidosis type VI (MPS VI or Maroteaux-Lamy syndrome) is a rare autosomal recessive genetic disorder. We treated a 10-year-old girl with Maroteaux-Lamy syndrome successfully with bone marrow transplantation (BMT).**

Methods: **The patient had reconstitution with bone marrow from her HLA-matched brother. One month after BMT, arylsulfatase activity of the recipient's leukocytes became normal. No graft-versus-host disease (GVHD) was observed. Arylsulfatase B activity was maintained and the urinary excretion of glycosaminoglycans (GAGs) became normal.**

Results: **The clinical response of the patient was slow but persistent during 12 years after BMT. Improved motor function included walking alone for a long distance without aid, riding a bicycle, taking a bath by herself, etc. Besides, few infections occurred. Exertional dyspnea, severe snoring, and vertigo were much improved.**

Conclusions: **Early intervention is recommended for BMT. Allogeneic BMT may provide a better life quality as illustrated in the present case.**

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Introduction

Mucopolysaccharidosis type VI (MPS VI; MIM#253200) or Maroteaux-Lamy syndrome is a rare autosomal recessive genetic disorder due to an inherited defect in arylsulfatase B activity (ASB, EC 3.1.6.12, or N-acetylgalactosamine-4-sulfatase), which in turn causes accumulation of dermatan sulfate and chondroitin sulfate within lysosomes in tissues.[1] This disease was first described by Maroteaux and Lamy et al[2] in 1963 as a Hurler-like (MPS I) disorder, but unlike MPS I, the intelligence was intact. Mutations within the gene encoding N-acetylgalactosamine 4-sulfatase may account for the disease. The severity of MPS VI depends on the levels of enzyme activity in various tissues involved.

MPS VI disease can be treated by bone marrow transplantation (BMT)[3] that corrects the patient's cells through the uptake of the normal enzyme secreted by bone marrow-derived cells especially macrophages or, as recently reported, by enzyme replacement therapy (ERT)[4] providing a source of a recombinant human arylsulfatase B. In this report, we describe the biochemical, cytogenetical and clinical findings in a 22-year-old female MPS VI patient, who received BMT 12 years ago when she was 10 years old.

Case report

A 10-year-old girl with Maroteaux-Lamy syndrome was admitted to the National Taiwan University Hospital for bone marrow transplantation in March 1995. She had decreased visual acuity and occasional right hand numbness at 3 years of age. At the same time, coarse face, flat nose, and corneal opacity were noted. Progressive joint deformity and stiffness due to contracture bothered this patient. Her echocardiogram showed mild mitral insufficiency. The diagnosis was established by the demonstration of low arylsulfatase B activity.[5] Her younger brother had normal enzyme activity.[6]

Her height was 115 cm, and weight was 19.5 kg. Body mass index was 14.7. Echocardiogram showed mitral valve prolapse with mild mitral valve regurgitation and stenosis. She could walk alone with limited range of motion. Bone and joint deformities in shoulders, elbows, wrists, knees, ankles and fingers were noted.

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Table 1. Clinical manifestations

Manifestations	Patient*					
	At diagnosis (July 1990)	1 mon before BMT (Feb 1995)	8 mon after BMT (Nov 1995)	3 y after BMT (July 1998)	5 y after BMT (May 2000)	after 9 y (Aug 2004)
Age	5 y	10 y	10 y 9 mon	13 y 5 mon	15 y 3 mon	19 y 6 mon
Bone or joint deformity	-	+	+	+	+	+
Recurrent severe infection	-	-	+	-	-	-
Snoring	+	+	+	Diminished	Diminished	Diminished
Walking	+	Family support	Alone	Alone	Alone	Alone
Riding a bicycle	+	Difficult	Slowly riding	Possible	Possible	Possible
Taking a bath	ND	Difficult	Possible alone	Possible alone	Alone	Alone
Shortened breath in exertion	ND	+	+	-	-	-

*: The basic data of this patient. ND: no data.

Besides, shortness of breath after exercise was also noted (Table 1).

The preparative regimen for transplantation consisted of busulfan (40 mg per meter square per dose q6 hours) 5 and 4 days before BMT, and cyclophosphamide (60 mg per kilogram) 3 and 2 days before BMT. Total lymphoid irradiation 750 cGy was given 1 day before BMT. Bone marrow was transplanted from the patient's HLA-match brother on day 0. Eleven days after transplantation, the patient had an absolute neutrophil count above 500. Subsequent blood counts were normal. The complications after transplantation included neutropenic fever, anemia and thrombocytopenia. No platelet transfusion was needed, but washed RBC "O" type was transfused once on day 21. No sign of acute or chronic graft-versus-host disease (GVHD) was observed. Cyclosporine A prophylaxis was tapered one year after transplantation.

The analysis of arylsulfatase B activity[5,6] employed p-nitrocatechol sulfate and barium acetate. Forty μg of leukocyte soluble protein was incubated with substrate and buffer at 37ºC. Iduronidase activity was determined as a control enzyme.[7] Urinary glycosaminoglycans (GAGs) concentration was determined according to the method reported by de Jong et al.[8] GAGs were determined quantitatively in urine by reaction with dimethylmethylene blue (DMB).

The donor was a male, and the recipient was a female. After engraftment, bone marrow biopsy study on day 21 revealed normal male karyotype of 46, XY. The peripheral blood FISH study showed 7 XX cells and 293 XY cells in 300 cells 9 years after transplantation. Besides, the following gene mutation analysis showed heterozygous mutation in the mucopolysaccharidosis gene (c574T>C (pCys192Arg)).

Arylsulfatase B in leukocytes was severely deficient 4 years and 1 month before bone-marrow transplantation (Table 2). One month after transplantation, leukocyte arylsulfatase B activity returned to normal and lasted for 12 years after BMT.

Table 2. Arylsulfatase B (ASB) activity in leukocytes before and after BMT in subjects with the Maroteaux-Lamy syndrome

Patients	ASB* (nmol/mg protein/h)	ASA (nmol/mg protein/h)	Iduronidase† (nmol/mg protein/h)
Before BMT			
4 y	30.5	ND	63
1 mon	25.23	129.59	55.43
After BMT			
1 mon	227.28	244.14	ND
4 y	584.71	165.01	ND
Brother (donor)	301.6	202.09	ND
Controls	215.9	129.13	ND

*: Activity was determined by p-nitrocatechol sulfate (p-NCS) containing barium acetate as substrate. ASB normal level >121 nmol/mg protein/h; ASA normal level >71.1 nmol/mg protein/h.
†: Iduronidase was used as control enzyme. Iduronidase normal level: 30 nmol/mg protein/h. ND: no data.

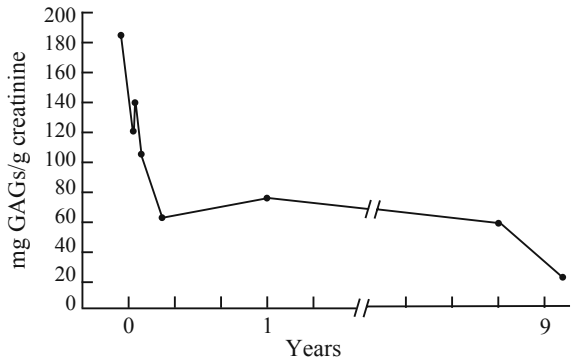

Fig. Urinary GAGs excretion decreased from elevated levels before BMT to normal one month after BMT. The normal value depended on age and her normal value is around 10-120 mg GAGs/g creatinine.

Urinary GAGs excretion decreased from elevated levels before BMT to normal one month after BMT (Fig.).[8]

The patient's height increased slowly after BMT. Her body mass index decreased from 14.7 to 13.6 and then increased to 16.6 gradually. General appearance including face and nose was stationary. The deformities of bone and joint were stable without progression, but she could ride a bicycle, and take a bath without help. Echocardiography and electrocardiography showed

no significant change in cardiac function. She had an episode of pulmonary infection. Snoring and vertigo were also significantly diminished. The improvement of motor function enabled her to take care of herself on daily activities. She is now studying at a university.

Discussion

BMT may be a good choice for the treatment of some storage diseases. However, the evaluation of the results of BMT is difficult because a small number of MPS VI patients have undergone the transplantation, and MPS VI is slowly progressed compared with the other storage diseases.[9]

In this case, normal bone marrow was engrafted for 12 years. Four years after the engraftment, arylsulfatase B activity of leukocytes remained normal. Persistent improvement was seen in the next 12 years, providing definite evidence that the donor bone marrow had engrafted in the recipient. In addition to biochemical improvement, her motor function, breath shortage while moving, and upper respiratory tract infections, and severe and frequent snoring were markedly improved after BMT. Her life quality has also improved. She can play with her classmates and give fair school performance. She can ride a bicycle and take a bath without help. But bone changes and joint deformity were not reversed prominently because of low penetration into the bone and joints or late BMT for her age.[10] In MPS VI patients treated with ERT, stored glycosaminoglycans are cleaned in major soft tissues except the cornea and articular cartilage. There are significant endurance in walking tests,[4] improvements of visual acuity and limited corneal clouding. The poor height gain in our patient may be attributed to uncorrected bone changes or endocrine complications after BMT.

Overall, BMT is a beneficial management for patients with MPS VI. It prolongs the life of the patient and inhibits many progressive manifestations of the disease, especially cardiac pathology and motor function.[4] These beneficial effects are sustained after long-term follow-up. Although BMT does not apparently reverse skeletal manifestations, the patient may remain active and walkable. The choice of BMT for candidates is complex because the clinical severity of MPS VI is persistent. In future, MPS IV patients should be completely evaluated to identify the most suitable timing for BMT before the occurrence of irreversible changes in organs.

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