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Case Report

Early enzyme replacement therapy enables a successful hematopoietic stem cell transplantation in mucopolysaccharidosis type IH: Divergent clinical outcomes in two Japanese siblings

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Abstract

Mucopolysaccharidosis type IH (MPS IH, Hurler syndrome) is a progressive, multisystem autosomal recessive lysosomal storage disorder resulting in the consequent accumulation of glycosaminoglycans. It is well recognized that early hematopoietic stem cell transplantation (HSCT) prevents neurocognitive decline in MPS IH. We followed the divergent clinical course in two Japanese siblings with MPS IH. The elder sister (proband) received a diagnosis of MPS IH at 6 months old. At the time of this diagnosis enzyme replacement therapy (ERT) was not available in Japan. She developed severe and recurrent respiratory disease and died at 1 year 10 months of age. Her younger sister also received a diagnosis of MPS IH, but at 18 days of age, and started ERT at 34 days of age. ERT continued until 8 months of age and prevented the progression of somatic manifestations of MPS IH. She received HSCT at 9 months old. Five years after HSCT she had no symptoms of MPS IH except for mild signs of dysostosis multiplex and mild cardiac valvular disease. Her neurological function was generally preserved compared with her elder sister. The prognosis and quality of life differed significantly between the sisters. Therefore, early HSCT can preserve neurocognition by preventing the neurodegeneration from MPS IH. In addition, ERT initiated during the asymptomatic period prevented the patient from developing somatic manifestations and enabled successful HSCT in this case.

Keywords: Hematopoietic stem cell transplantation; Enzyme replacement therapy; Mucopolysaccharidosis type IH; Central nervous system deterioration

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1. Introduction

Mucopolysaccharidosis type IH (MPS IH, Hurler syndrome, MIN: 607014) is a lysosomal storage disease due to a congenital deficiency of lysosomal enzyme alpha-L-iduronidase (IDUA). The consequent accumulation of dermatan sulfate and heparan sulfate in lysosomes in a wide range of tissues results in significant functional impairment and a shortened lifespan. Patients with the severe subtype (MPS IH) exhibit nonspecific manifestations (e.g., umbilical or inguinal hernia, frequent upper respiratory tract infections), progressive respiratory, cardiac, and musculoskeletal symptoms (dysostosis multiplex) beginning in infancy, along with progressive cognitive decline that usually becomes apparent by 2 years of age. Untreated children usually die before 10 years of age due to cognitive decline, combined with progressive pulmonary and cardiac dysfunction [1]. Enzyme replacement therapy (ERT) with laronidase (recombinant human α-L-iduronidase; Aldurazyme®, Sanofi Genzyme and BioMarin Pharmaceutical) is safe and effective in patients with MPS IH. ERT led to clinically significant reduction of hepatomegaly and improvements in pulmonary function, endurance, mobility, and quality of life [2]. However, ERT is ineffective for treatment of the neurological disease because the intravenously administered enzyme does not penetrate the blood-brain barrier. On the other hand, hematopoietic stem cell transplantation (HSCT) is effective for preventing the progression of central nervous system (CNS) deterioration. The outcome of HSCT for MPS IH depends on the age and the degree of CNS deterioration present at the time the patient received HSCT. To maximize the clinical benefit of HSCT, transplantation should be performed before 2 years of age and the developmental quotient/intelligence quotient (DQ/IQ) should be 85 or more [3–5]. A previous report showed that ERT prior to HSCT improved the physical condition in patients with MPS IH and could reduce transplant-related mortality and morbidity [4]. Pre-transplant ERT improved the patient's condition before HSCT and may have enhanced the beneficial effect of HSCT. Therefore, a European modified Delphi expert panel recommended starting ERT at diagnosis in young MPS IH patients and performing HSCT as soon as possible thereafter. It was shown that ERT prior to HSCT was well tolerated and may have significantly improved the pre-transplant condition in patients with MPS IH in this study.

In this article, we report our treatment experience with two Japanese sisters with MPS IH. They had a common background including sex, and ethnic, genetic, and environmental factors. Therefore, a direct comparison of prognosis between the sisters strongly supported the concept that ERT prior to HSCT can prevent the progression of somatic symptoms of MPS IH and that HSCT at an early stage can preserve neurocognition.

2. Subjects

2.1. Patient 1 (elder sister, the second child) and patient 2 (younger sister, the fifth child)

Patient 1 is the second child in this pedigree. Patient 1 was admitted to the NICU due to respiratory distress after birth. Shortly after leaving the hospital, her respiratory condition worsened due to respiratory syncytial virus infection at 3 months of age. At that time, chest X-ray showed that she had dysostosis multiplex. She received a diagnosis of MPS IH by undetectable IDUA activity in leukocytes at 6 months of age. Patient 2 is the fifth child in this pedigree. Ectopic and unusually widely distributed Mongolian spots, in addition to the family history, strongly supported the diagnosis of MPS IH. She received a diagnosis of MPS IH by measurement of enzyme activity of umbilical cord blood at 18 days old. IDUA activity of lymphocytes was $\leq$0.8 nmol/mg protein/hr (normal range: 28.8–89.8 nmol/mg protein/hr). After obtaining informed consent for participation in this study and gene analysis from patient's parents, mutation analysis of the *IDUA* gene was performed. It revealed two frameshift mutations, c.164-165insC (p.L56AfsX8) and c.1395delC (p.G466AfsX60). Genetic testing of the parents showed that these mutations existed on different alleles. Gene analysis of IDUA was approved by the ethical committee of National Center for Child Health and Development (Approved study number; 375).

3. ERT, HSCT, and clinical assessment

Patient 1 was not able to receive ERT because laronidase was not available in Japan. As her general condition, and respiratory function in particular, were poor, she underwent home oxygen therapy. Due to chronic pulmonary dysfunction and recurrent respiratory infection, the implementation of HSCT was not considered. Patient 2 started ERT with laronidase from 34 days after birth. ERT continued until she was 8 months old. Then she received HSCT from her HLA-8/8 allele (HLA-A, HLA-B, HLA-C, and HLA-DRB1) matched elder sister (the fourth child in the pedigree) at 9 months old. Before performing HSCT, the fourth child was received genetic testing after obtaining informed consent from the parents and was confirmed as neither affected nor a carrier. The conditioning regimen comprised busulfan (19.2 mg/kg), cyclophosphamide (200 mg/kg), and anti-thymocyte globulin (5 mg/kg; Genzyme). Prophylaxis against graft-versus-host disease (GVHD) was implemented by administering cyclosporine A (3 mg/kg/day). Granulocyte colony-stimulating factor at a

dose of 5 μg/kg was administered from post-transplantation day 5 until a neutrophil count $>1.5 \times 10^9$/L was achieved. On day 0, 8.9×10^8/kg bone marrow nucleated cells (13.8×10^6/kg bone marrow CD34-positive cells) were infused via a central venous catheter. A neutrophil count $>0.5 \times 10^9$/L and a reticulocyte count $>20 \times 10^9$/L were achieved at days 11 and 15, respectively. Donor cell engraftment was examined by the short-tandem-repeat (STR) method, and 100% of the donor-type cells were detected by using bone marrow cells collected on day 56. At the final chimerism study undertaken 5 years post-transplant using peripheral blood granulocytes, T-cells and NK cells showed 100% donor type. Both acute and chronic GVHD were not observed. Periodic clinical laboratory tests and physical examinations were performed every 12 or 18 months. DQ was assessed with the Kyoto Scale of Psychological Development (2001) [6].

Table 1
Comparison of developmental milestones and clinical symptoms between patients 1 and 2.

	Patient 1	Patient 2
Holds head steady	4 m	4 m
Sits without support	10 m	8 m
Stands with help	11 m	9 m
Walks well	1 y, 8 m	1 y, 2 m
Speaks first words	11 m	1 y, 2 m
Puts two words together	None	1 y, 7 m
Oxygen administration	Home oxygen therapy	None
Umbilical hernia	Sustained	Healed at 1 y, 6 m
Final observation	1 y, 10 m (died)	5 y, 8 m

Abbreviations: m, months of age; y, years of age.

4. Results

In patient 1, motor development was moderately delayed. She was not able to walk alone at 1 year and 8 months of age. She began to say single words like "mama" at 1 year and 8 months of age (Table 1). Patient 1 demonstrated typical MPS IH facial changes at 1 year of age (Fig. 1A). She died of a respiratory infection at 1 year and 10 months of age.

In contrast to patient 1, patient 2 did not develop coarse facial features (Fig. 1B). The motor milestones were within normal range for her age. She had no skeletal problems, joint contractures, or claw hands (Fig. 1C). An echocardiogram demonstrated mild regurgitation of the mitral valve and aortic valve. Mild defective development of the vertebral bodies with abnormal egg-shape and anterior beak signs with oar-shaped ribs

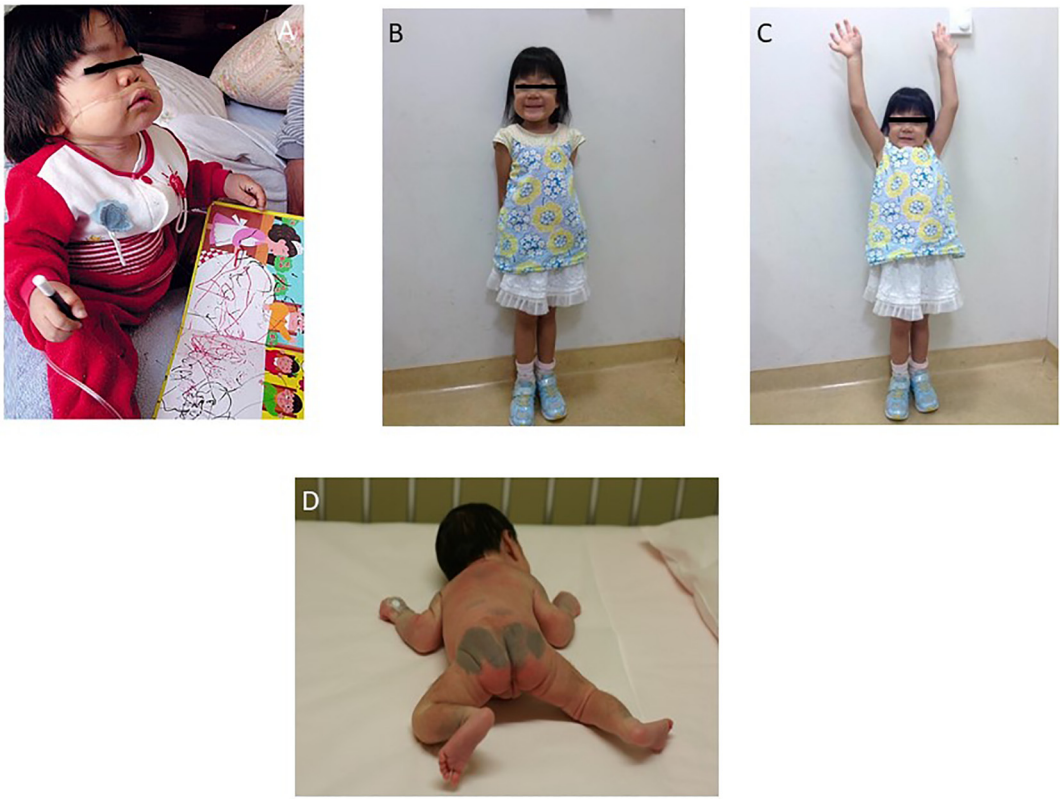

Fig. 1. Coarse facial features in patient 1 at 1 year old. She exhibited typical MPS IH facial appearance, including a broad nose with a flat bridge and wide upturned nostrils. She also had joint contractures of the fingers (A). Facial and physical appearance of patient 2 at the age of 5 years and 8 months (B). She exhibited normal facial and physical appearance. Joint range of motion of the shoulders was within normal range (C). Mongolian spots on the back and buttocks of patient 2 at birth (D). The patients' parents provided written consent for use of photographs in this publication.

had been observed from birth (Fig. 2A, B), and the changes remained after 3 years of HSCT (Fig. 2D, E). Radiographs of the hands in patient 2 at birth showed no metacarpal pointing or bullet-shaped phalanges (Fig. 2C); however, she showed apparent point-shaped metacarpal bones after 3 years of HSCT (Fig. 2F). Brain MRI at 5 years old showed a small perivascular space around the dorsal ventricular horn, but no apparent ventricular dilation or brain atrophy. Her developmental milestones were almost normal (Table 1). Her DQ values of 87, 88, and 84 were within normal range when assessed at 3 years and 2 months of age, 4 years and 2 months of age, and 5 years and 8 months of age, respectively. At age 5 years, IDUA activity of lymphocytes was 46.6 nmol/mg protein/hr (normal range: 28.8–89.8 nmol/mg protein/hr) and urine uronic acid level was 23.6 mg/g creatinine (normal range: 26.4 ± 8.1 mg/g creatinine at 5 years old). Normal leukocyte IDUA enzyme activity and urine uronic acid levels were maintained after HSCT.

5. Discussion

In this study, we reported that HSCT following ERT showed apparent clinical improvement in the younger sister (patient 2) compared with her elder sister (patient 1). These results strongly suggest that HSCT following ERT initiated at an early stage can preserve cognition and ameliorate some of the somatic manifestations of MPS IH. In addition, early initiation of ERT with laronidase presumably enabled a successful HSCT. As ERT has been shown to result in a significant and relatively rapid improvement in respiratory and cardiovascular function [2], ERT may have ameliorated the pre-transplant condition of patient 2. There have been concerns that exposure to exogenous laronidase ERT may stimulate the production of neutralizing antibodies against this enzyme that could cause graft failure and increase the risk of graft-versus-host disease [7,8]. In this study, antibody status was determined by an enzyme-linked immunosorbent assay (ELISA). Patient 2 developed IgG antibody to laronidase at a titer of 1:100 after 6 months of ERT. There were no infusion-related reactions during ERT treatment and engraftment was successful. In patient 2, antibody production against laronidase showed little negative effect on HSCT.

Patients with MPS IH usually receive this diagnosis after presenting with a combination of somatic manifestations and neurodegeneration. Therefore, the important role of newborn screening (NBS) for MPS IH is emphasized. The Secretary of Health and Human Services in the USA has recommended that MPS IH should

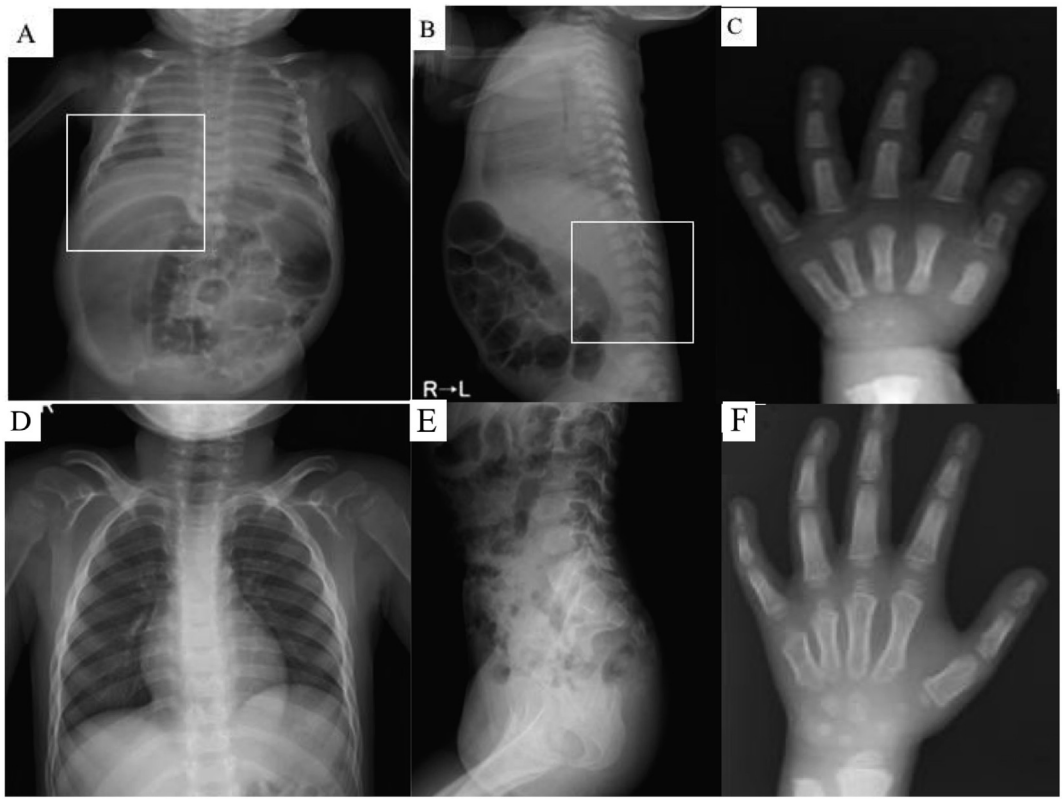

Fig. 2. Radiographic findings of ribs, spinal column, and hands at birth (A–C) and after 3 years of HSCT (D–F) in patient 2. Mild dysostosis multiplex in ribs and vertebral bodies was observed in patient 2 at birth. The results remained unchanged after HSCT. Radiograph of findings of hands were normal finding at birth and were progressed after HSCT. The patients' parents provided written consent for use of photographs in this publication. The patients' parents provided written consent for use of photographs in this publication.

be added to the Recommended Uniform Screening Panel. The NBS programs for MPS IH in Taiwan and several states in the United States have already started [9,10]. NBS is effective as a means for the early detection of progressive diseases. In most countries, including Japan, NBS for MPS I is not available, and it will take time to come into practice. Alternatively, ectopic and dark Mongolian spots may be a clue to consider the diagnosis of MPS. As shown in Fig. 1D, unusually large and widespread Mongolian spots with dark color were observed in patient 2 during the newborn period. These unusual Mongolian spots may be a clue to consider patients with MPS in Asian ethnic newborns. Currently, novel treatments for MPS IH, including ERT with a blood-brain barrier penetrating recombinant enzyme and gene therapy, are being developed. It will be important to select the best treatments for MPS IH patients who have received the diagnosis by NBS at an early stage.

Ethics approval

Ethics approval and consent to participate and publish: Gene analysis of IDUA was approved by the ethical committee of National Center for Child Health and Development. Provided approval for use of the case including patients' pictures. The patients' parents provided written consent for use of data in this publication.

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Authors' contributions

NY, MK, KK, GT, YF, HM, MS, and AH provided patient data, MK, TO, and AI were involved in assessing and interpreting data, and all authors participated in manuscript development and writing.

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