Molecular Genetics and Metabolism Reports 2 (2015) 65–76

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: http://www.journals.elsevier.com/molecular-genetics-and-metabolism-reports/

Long-term follow-up of post hematopoietic stem cell transplantation for Hurler syndrome: Clinical, biochemical, and pathological improvements

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ARTICLE INFO

Article history:
Received 24 December 2014
Accepted 24 December 2014
Available online 23 January 2015

Keywords:
Hurler syndrome
HSCT
Skeletal dysplasia
Cognitive function
ADL

ABSTRACT

Mucopolysaccharidosis type I (MPS I; Hurler syndrome) is a lysosomal storage disease caused by a deficiency of the enzyme α-L-iduronidase which affects multiple organs such as central nervous system (CNS), skeletal system, and physical appearance.

Hematopoietic stem cell transplantation (HSCT) is recommended as a primary therapeutic option at an early stage of MPS I with a severe form to ameliorate CNS involvement; however, no description of pathological improvement in skeletal dysplasia has been investigated to date.

We here report a 15-year-old male case with MPS I post-HSCT. This patient received successful HSCT at the age of 2 years and 1 month, followed for over 10 years. His activity of daily living including cognitive performance has been kept normal and the present height and weight are 162 cm and 55 kg. Bone deformity has been still developed, resulting in hemiepiphysiodesis of bilateral medial proximal tibia at 12 years of age and successive arthrodesis of thoraco-lumbar spine at 13 years of age; however, skeletal histopathology from surgical remnants showed substantial improvement in bone lesion with markedly reduced occurrence and cell size of vacuolated cells. After a series of surgical procedures, he became ambulant and independent in daily activity. The levels of GAGs in blood were substantially reduced.

In conclusion, this long-term post-HSCT observation should shed light on a new aspect of therapeutic effect associated with skeletal pathology and GAG levels as a biomarker, indicating that HSCT is a primary choice at an early stage for not only CNS but also skeletal system in combination of appropriate surgical procedures.

1. Introduction

Mucopolysaccharidoses (MPS) are a group of 11 lysosomal storage diseases caused by a deficiency of enzymes that degrade glycosaminoglycans (GAGs), leading to accumulation of GAGs in multiple tissues.

Mucopolysaccharidosis type I (MPS I) has historically been divided into three phenotypes according to the clinical severity; a severe form — Hurler syndrome (MPS IH), an intermediate form — Hurler/Scheie syndrome (MPS IH/IS), and a mild form — Scheie syndrome (MPS IS) [1,2]. MPS I is an autosomal recessive disorder, caused by mutations in the α-L-iduronidase (IDUA) gene. The resultant IDUA

Abbreviations: AB, alcian blue; AB/PAS, alcian blue/periodic acid–Schiff; ADL, activity of daily living; AIDHC, Alfred I. duPont Hospital for Children; BMI, body mass index; BMT, bone marrow transplantation; CDC, the centers for disease control and prevention; CI/VG, colloidal iron/van Gieson; CNS, central nervous system; DS, dermatan sulfate; ECM, extracellular matrix; EM, electron microscopy; ERT, enzyme replacement therapy; GAG, glycosaminoglycan; HE, hematoxylin and eosin; HS, heparan sulfate; HSCT, hematopoietic stem cell transplantation; IDUA, α-L-iduronidase; IRB, institutional review board; IS, internal standard; LC–MS/MS, liquid chromatography–tandem mass spectrometry; LM, light microscopy; MPS, mucopolysaccharidoses; MPS I, mucopolysaccharidosis I; QOL, quality of life; Saf. O/FG, safranin O/fast green.

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http://dx.doi.org/10.1016/j.ymgmr.2014.12.006

deficiency generates the progressive accumulation of undegraded GAGs, dermatan sulfate (DS) and heparan sulfate (HS) in lysosome and extracellular matrix (ECM), leading to apoptosis of cells and successive organ dysfunction. IDUA deficiency is characterized by multisystemic disease, and thus produces a wide range of clinical manifestations. Clinical features in patients with MPS I include dysostosis multiplex, corneal clouding, hepatosplenomegaly, and airway obstruction as well as central nervous system (CNS) involvement.

MPS I as well as other types of MPS result in premature morbidity and mortality. Enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT) have been conducted as a primary therapeutic option for MPS I.

Intravenous ERT reverses some aspects of MPS I (e.g., hepatomegaly, splenomegaly and glycosaminoglycanuria) and ameliorates others (e.g., pulmonary function, cardiac disease, arthropathy and exercise tolerance). However, neurologic benefits are thought to be negligible because the blood brain barrier (BBB) blocks enzyme from reaching the CNS. At present, while available for some conditions, exogenous ERT cannot correct cognitive and CNS disease [3,4].

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. HSCT has been performed on patients with MPS IH, resulting in clinical improvement of somatic manifestations and cognitive function if it is completed under 2 years of age [5,6]. Tanaka et al. has 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 [7]. HSCT also shows some benefits in physical activity and growth. Those studies state that allogeneic HSCT could be potential primary care for MPS I, MPS II [7,8], and MPS VII [9].

Thus, introduction of HSCT at an early stage of the disease maintains or ameliorates the neuro-cognitive functions associated with MPS [3].

Accumulated cases support that morbidity, quality of life (QOL), and survival in these patients can be improved by allogeneic HSCT [3]. Especially, HSCT is effective when it is introduced to the patients with MPS IH before 2 years of age with over 80 of IQ score. Early HSCT has been recognized as the standard of care for patients with the severe phenotype of MPS I.

HSCT of patients with MPS I improves QOL with restoration of CNS involvement; however, therapeutic effect remains unknown in bone pathology [10]. Skeletal manifestations observed in MPS IH has been known as dysostosis multiplex [3–6], consisting of abnormally shaped vertebrae and ribs, enlarged skull, spatulate ribs, hypoplastic epiphyses, thickened diaphyses, bullet-shaped metacarpals, hip dysplasia, genu valgum, and spinal cord compression [7].

There are several reports on skeletal and growth improvement post-HSCT on MPS I [11–24]. With successful engraftment, substantial clinical improvements of joint mobility, coarse facial features, and claw hands were reported [21]. Meanwhile, the skeletal manifestations still seem to provide a problem in the QOL in transplanted patients with MPS IH [19]. With age, clinical and radiographic musculoskeletal abnormalities still developed. This is presumably due to the limited penetration of the expressed enzyme into the bone, especially cartilage [14]. However, there has been no report on bone pathology in post-HSCT patients with MPS IH.

DS and HS (primary storage materials) and KS (secondary storage material) have been proposed to be surrogate biomarkers for MPS I [25]: however, to date no report has been described on improvement of skeletal pathology and relevant biomarker.

Until now, we have no clear answer of how extent the enzyme secreted from engrafted stem cells penetrate and fix the bone lesion in correlation with reduction of storage materials (GAGs).

In this report, we first describe the clinical history and improvement in bone histopathology and relevant biomarker as well as CNS and skeletal manifestations after over 10 years post-HSCT in a male patient with MPS IH.

2. Material and methods

2.1. Case report

2.1.1. Initial clinical course

The patient was born at a full term via a C-section because of a failure of the normal delivery to progress. Birth weight was 4224 g (above 90th percentile), and birth length was 54.6 cm (above 95th percentile) of age compared with control subjects from the centers for disease control and prevention (CDC), suggesting that the present case has excessive growth at birth as described previously in patients with MPS I [26]. His mother initially noticed the clinical problems of kyphosis and corneal clouding at 2 months of age, and these clinical features were pointed out at every pediatric physical check-up. The initial findings in this case include bone deformity, failure of thrive, kyphosis, scoliosis, abnormal gait, difficulty of joint movement, umbilical and inguinal hernias, knee problem, corneal clouding, chronic ear infections, short neck, and heart murmur. In MPS IH, developmental delay is often apparent by 12 to 24 months of age [2] while in Hurler–Scheie syndrome, onset of symptoms occurs between ages 3 and 8 years [2].

With the progression of the disease, he was diagnosed as MPS IH at 11 months of age, and underwent cord blood transplantation at Duke University at the age of 2 years and 1 month before CNS involvement became prominent [6]. α-L-Iduronidase enzyme activity in peripheral-blood leukocytes was 0.16 nmol/h/mg of protein (normal level: 30–70 nmol/h/mg of protein). The patient had a cord blood transplant with an A+, male, 5/6 matched cord blood units with mismatch at the B locus. The total mononuclear cell dose was 5.6×10^7 cells/kg. The patient had the full engraftment with grade I GVHD, and the enzyme activity was normalized to 57.8 nmol/h/mg of protein after HSCT.

With age, he underwent surgical procedures of adenoidectomy, tonsillectomy, and multiple myringotomy tube placements. This patient was referred to Alfred I. duPont Hospital for Children (AIDHC) for evaluation of progressive bilateral hand weakness at the age of 5 years. He had locking of both hands since the age of 11 months and had possible trigger fingers and carpal tunnel syndrome, both of which are common in children with MPS I. He did not complain of pain or paresthesias; however, his hands were stiff in the morning.

2.1.2. Orthopedic surgical history

Until the age of 6.5 years, the patient had no significant scoliosis; however, a kyphotic deformity at the thoracolumbar junction secondary to hypoplasia of L2 and retrolisthesis of L2. Diffuse bony changes of dysostosis multiplex were evident (Fig. 1). There was no leg length discrepancy; however, genu valgum was present bilaterally.

At 7 years and 7 months of age, the alignment of cervical spine was anatomic. No instability of the cervical spine was observed. The vertebrae have an oval configuration consistent with MPS I. The odontoid was mildly decreased in height (data not shown). Kyphotic deformity at the thoracolumbar junction was not significantly changed. Mild deformity of the anterior margin of the lumbar vertebral bodies appeared stable without scoliosis. The femoral heads well seated bilaterally in small acetabula.

At the age of 12 years, the cervical spine remained stable, although the vertebrae were mildly flattened and elongated with an oval shape and the odontoid was hypoplastic. The atlantodental interval was stable in neutral, flexion, and extension positions, consistent with no instability. Cervical alignment remained stable in all positions. Until 12 years of age, bilateral genu valgum remained stable, and reduced acetabular coverage was observed bilaterally. The patient had a gibbous deformity with the apex of the kyphotic curve at L2. There was retrolisthesis of L3 on L4 (Fig. 2).

At the age of 12 years and 5 months, the bones of the cervical spine were properly corticated. There was no evidence of atlantoaxial instability with mild dysmorphic changes of the odontoid. Dysmorphic changes of the cervical vertebrae were observed with widening of the disc spaces