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Impact of enzyme replacement therapy and hematopoietic stem cell therapy on growth in patients with Hunter syndrome

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ABSTRACT

Patients with Hunter syndrome (mucopolysaccharidosis II) present with skeletal dysplasia including short stature as well as CNS and visceral organ involvement. A previous study on Hunter syndrome indicated an impact on brain and heart involvement after hematopoietic stem cell therapy (HSCT) at an early stage but little impact after enzyme replacement therapy (ERT) (Tanaka et al. 2012). Meanwhile, impact on growth in patients with Hunter syndrome treated with ERT and HSCT has not been compared until now. We recently developed baseline growth charts for untreated patients with Hunter syndrome to evaluate the natural history of growth of these patients compared to unaffected controls (Patel et al., 2014).

To assess impact of ERT and HSCT on growth, clinical data were obtained from 44 Japanese male patients with MPS II; 26 patients had been treated with ERT, 12 patients had been treated with HSCT, and 6 had been treated

Abbreviations: DS, dermatan sulfate; ECM, extracellular matrix; ERT, enzyme replacement therapy; GAG, glycosaminoglycan; HSCT, hematopoietic stem cell therapy; HS, heparan sulfate; I2S, iduronate 2-sulfatase; LSD, lysosomal storage disorder; MPS II, mucopolysaccharidosis II.

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with both ERT and HSCT. Height and weight were compared to untreated patients and unaffected controls from the previous study.
We demonstrated 1) that MPS II patients, who had been treated with either ERT or HSCT, had increased height and weight when compared to untreated patients, and 2) that HSCT and ERT were equally effective in restoring growth of MPS II patients.
In conclusion, HSCT should be considered as one of the primary therapeutic options for early stage treatment of MPS II, as HSCT has also been reported to have a positive effect on brain and heart valve development (Tanaka et al. 2012).

1. Introduction

Mucopolysaccharidosis II (MPS II, Hunter syndrome; OMIM #309900) is a lysosomal storage disorder (LSD) caused by a mutation in the X-linked gene IDS. This results in deficiency of the lysosomal enzyme, iduronate 2-sulfatase (I2S), in the metabolic pathway that leads to degradation of the glycosaminoglycans (GAGs), dermatan sulfate (DS) and heparan sulfate (HS) [1]. This enzyme deficiency blocks the stepwise degradation of DS and HS, resulting in the accumulation of DS and HS in lysosomes and extracellular matrix (ECM) of a wide range of tissues. Although the primary result of enzymatic deficiency is accumulation of GAGs and secondary substrates, the mechanism causing the pathogenesis of the disease still remains unknown [2]. MPS II has a prevalence rate between 1:100,000 and 1:170,000 male births [3,4], and is the most prevalent form of MPS disorders in Asian countries where it accounts for around 50% of all MPS cases diagnosed [5].

Patients with MPS II have a wide range of symptoms caused by the disease that affect multiple different organ systems. The severe phenotype is more than twice as prevalent as the attenuated form of the disease, and is characterized by profound CNS involvement and is usually fatal in early childhood if not treated [6]. Patients with the attenuated phenotype may survive into adulthood without CNS involvement [1,7].

Inguinal and/or umbilical hernia, course facial features, otitis and nasal obstruction along with recurrent upper respiratory tract infections are some of the early diagnostic cues in MPS II [8]. Extensive and aberrant Mongolian spot is also a characteristic finding of Hunter syndrome in Japan [9]. The skeletal abnormalities in MPS II are similar regardless of clinical phenotype, and are common among other types of MPS disorders. The skeletal abnormalities are characterized in general as a thickening of the long bones with irregular ossification centers [1].

The major causes of morbidity and mortality in patients with MPS II are due to abnormal heart development; 82% of patients have cardiovascular signs and symptoms [1]. Detrimental CNS involvement in MPS II manifests most often as progressive cognitive degeneration, although individuals with the attenuated form of the disease have minimal CNS involvement. Patients may be able to reach early developmental milestones; however, psychomotor delays usually occur during the late infantile period [1]. Surgical procedures to correct inguinal and/or umbilical hernia are often performed before the diagnosis of Hunter syndrome [10].

There are currently two major therapies for patients with MPS II; enzyme replacement therapy (ERT) and hematopoietic stem cell therapy (HSCT).

ERT has been used to treat several types of MPS disorders, and for MPS II a recombinant form of human I2S is used (idursulfase, Elaprase®, Shire Human Genetic Therapies, Inc., Lexington, MA, USA). Clinical trials have shown that ERT decreases urinary GAG levels and improves measures of pulmonary function, walking ability, and visceral organ function [11–14]. Several limitations for conventional ERT have been noted: 1) limited efficacy for hard connective tissues including bone and heart valves due to avascularity of these tissues, 2) difficulty in compliance due to required 4–5 hour intravenous infusions every week, and 3) the high cost of treatment. Moreover, the enzyme cannot pass through the blood–brain barrier, and conventional ERT will have no effect on the CNS aspects of the disease [1,2,15,16].

Results from the Hunter Outcome Survey (HOS) show that response to treatment is not associated with either clinical phenotype or age at initiation of treatment [11]. MPS II patients treated with ERT continued to grow; however, their growth was not directly compared to untreated patients [11,17].