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Treatment reduces or stabilizes brain imaging abnormalities in patients with MPS I and II

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ABSTRACT

Background: The mucopolysaccharidoses (MPSs) are a family of lysosomal storage disorders caused by impaired glycosaminoglycan degradation. Characteristic brain imaging abnormalities are seen in MPS patients. This study aims to determine the effects of hematopoietic stem cell transplantation (HSCT) and/or intravenous enzyme replacement therapy (ERT) on these abnormalities.

Methods: A retrospective chart and brain imaging study review was conducted of MPS types I and II patients with brain magnetic resonance imaging (MRI) performed at, and following, initiation of treatment. White matter abnormalities, dilated perivascular spaces, corpus callosal abnormalities, and ventriculomegaly were scored by three independent neuroradiologists blinded to cognitive status, date of treatment initiation, and type(s) of treatment.

Results: Five patients were identified: three patients with MPS I and two with MPS II. Duration of follow-up ranged from 13 to 51 months. One patient had severe MPS I (genotype W402X/35del12) and received ERT followed by HSCT. The remaining patients had ERT only. The other two MPS I patients were cognitively normal siblings (genotype P533R/P533R) with an intermediate phenotype. One MPS II patient had moderate cognitive impairment without regression (genotype 979insAGCA); the other (genotype R8X) had normal cognition.

Results: There was very little inter-observer variation in MRI scoring. The greatest abnormalities for each patient were found at initial MRI. All patients, including the ERT-only patients, demonstrated improved or unchanged MRI scores following treatment. Severity of white matter abnormalities or dilated perivascular spaces did not correlate with cognitive impairment; as such, extensive pre-treatment MRI abnormalities were noted in the older, cognitively normal MPS I sibling. In comparison, his younger sibling had only mild MRI abnormalities at the same age, after receiving 4 years of ERT.

Conclusions: This study represents one of the first to document the CNS effects of ERT in MPS patients utilizing serial brain MR imaging studies, and raises several important observations. Brain MRI abnormalities typically become more pronounced with age; initiation of ERT or HSCT reversed or stabilized this trend in the MPS patients studied. In addition, earlier initiation of treatment resulted in decreased severity of imaging abnormalities. Possible mechanisms for these observations include improved cerebrospinal fluid dynamics, reduced central nervous system glycosaminoglycan storage via efflux through the blood–brain barrier (BBB), repair of damaged BBB, reduction in CNS inflammation, or ERT permeability through the BBB.

Introduction

The mucopolysaccharidoses (MPSs)[1] are a group of seven inborn errors of metabolism related by a deficiency in one of eleven lysosomal hydrolases that catalyze the stepwise degradation of glycosaminoglycans (GAGs). As a result of the enzyme deficiency, GAGs that are normally recycled in a healthy individual cannot be degraded in the MPS patient. Types I and II MPS are caused by deficiencies in α-iduronidase [IDUA, E.C. 3.2.1.76] and iduronate-2-sulfatase

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[1] *Abbreviations used:* BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; ERT, intravenous enzyme replacement therapy; GAG, glycosaminoglycan; HSCT, hematopoietic stem cell transplantation; IDUA, α-iduronidase; IDS, iduronate-2-sulfatase; MPS, mucopolysaccharidosis; MRI, magnetic resonance imaging; PVS, perivascular space; WM, white matter.

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[IDS, E.C. 3.1.6.13], respectively. Lack of either enzyme leads to symptoms derived from storage of heparan sulfate, a GAG found predominantly in the central nervous system, and dermatan sulfate, found in connective tissues throughout the rest of the body. Patients with severe MPS I, also known as MPS I-H (OMIM 607014), or severe MPS II (OMIM 309900) typically have cognitive impairment characterized by developmental stagnation and eventual loss of previously acquired milestones. Other MPS patients have an attenuated cognitive phenotype ranging from normal intelligence, to developmental delay without regression. These patients are described as having moderate or attenuated MPS I or II. Attenuated MPS type I is also known as MPS I-HS (OMIM 607015) or MPS I-S (OMIM 607016). The incidence of MPS I is estimated to be 1 in 150,000 live births; MPS II is seen in 1 in 150,000 to 200,000 male live births [1,2].

Scoring systems for MPS patients have been published that quantitated the severity of brain magnetic resonance imaging (MRI) abnormalities and attempted to correlate those abnormalities with severity of cognitive involvement. The most common abnormalities found on brain MRI are white matter (WM) lesions; dilated perivascular spaces (PVS) in the brain parenchyma, basal ganglia, corpus callosum, and brainstem; atrophy; and ventriculomegaly [3,4] . Studies agree that severity of PVS dilatation does not correspond with the degree of cognitive impairment [5–7]. The relationship between WM abnormalities and cognitive impairment is less clear. T2-weighted hyperintense white matter signals, at times severe enough to resemble leukodystrophy, have been reported in MPS patients with normal intelligence [4,7–9] as well as in MPS type VI, which does not affect intelligence [3]. Other studies did find quantitatively more severe WM alterations in MPS patients with mental retardation [6]. A statistically significant proportion of MPS II patients with cognitive involvement had severe white matter lesions compared to those without cognitive involvement [10]. The same studies demonstrate a steady trend of worsening MRI abnormalities with increasing age [5,11].

Intravenous enzyme replacement therapy (ERT) of the missing lysosomal hydrolase has been developed for MPS I (recombinant human α-iduronidase, rhIDUA, Aldurazyme®, Genzyme Corporation) and MPS II (recombinant human iduronate-2-sulfatase, rhIDS, Elaprase®, Shire HGT). Preclinical work in the canine MPS I model found reduced GAG levels and a small amount of IDUA activity in brain tissues following ERT, although no ultrastructural reduction in lysosomal storage was seen in the brain. The changes were attributed to possible sequestration of rhIDUA in the capillary endothelium [12]. Eventually, results from human clinical trials concluded that the enzymes' polarities and large molecular weights prevented blood–brain barrier (BBB) permeability [13,14]. Consequently, the intravenous route is not effective for the treatment of central nervous system (CNS) disease in severe MPS I or II patients. Hematopoietic stem cell transplantation (HSCT), however, appears to be able to rescue neurocognitive outcomes if performed early enough in patients with severe MPS I. This is thought to be due to the ability of the transplanted monocytes to infiltrate into the recipient CNS and secrete functional α-iduronidase [15]. The HSCT experience with severe MPS II patients has been disappointing. Affected boys continue to display cognitive decline, possibly because they are recognized and transplanted later than MPS I children [16,17].

Several studies have documented a positive effect of HSCT on WM abnormalities and ventriculomegaly [18,19]. Due to the presumed lack of efficacy of intravenous enzyme replacement therapy (ERT) upon the CNS, no studies utilizing serial brain MRI examinations to determine the effect of ERT in MPS I and II patients have been performed. This study reports the results of serial MRI examinations and abnormality scoring in one MPS I patient who received ERT and HSCT, and four other patients (2 MPS I and 2 MPS II) who received ERT.

Methods

Subject recruitment

A retrospective chart and brain MRI study review was conducted of mutation-proven MPS I and II patients at Children's Hospital of Orange County. To be included in this study, patients needed to have more than one brain MRI study, with the first study performed within a year of initiation of ERT and/or HSCT. All studies were performed with parental consent.

Imaging techniques

All MRI studies were performed with and without gadolinium contrast. The studies were performed using Siemens 1.5 T Avanto, Symphony, or Avanto Magnetom magnets. For the purposes of scoring, the following image series were utilized: sagittal 5 mm thick spin-echo T1-weighted, axial 5 mm thick spin-echo T1-weighted, axial 5 mm thick fast-spin echo T2-weighted, and axial 5 mm thick fluid-attenuated inversion recovery sequences.

Imaging evaluation

All imaging studies reviewed independently by 3 neuroradiologists (KO, JCF, DSK), who were aware only of the patients' ages and existence of mucopolysaccharidosis, but blinded to specific MPS diagnosis, cognitive status, type of treatment, and date of treatment initiation. The exact scoring methods for white matter signal changes, perivascular space dilatation, involvement of the corpus callosum, and ventriculomegaly are summarized in Table 1. A composite score for each study was obtained by totaling the scores for each category, for a maximum score of 30.

Results

Ten patients with MPS I or II were followed at Children's Hospital of Orange County. Of those, five (3 MPS I, 2 MPS II) had multiple brain MRI studies with the first study taking place within a year of treatment initiation. Four of the five had pre-treatment imaging. Patient 2 had his first brain MRI performed 7 months following initiation of ERT. MRI studies for each patient were obtained approximately every 12 months; follow-up duration ranged from 13 to 51 months. The specific clinical, biochemical, and treatment characteristics for each patient are detailed below.

Patient 1

She was diagnosed with severe MPS I (MPS I-H) at 12 months of age after thoracolumbar gibbus and dysostosis multiplex were noted. Initial plasma IDUA activity was undetectable (normal >38 nmol/mg/h protein) and urine GAG concentration was 89.0 mg/mmol creatinine (normal <12.3). *IDUA* mutation analysis showed compound heterozygous W402X/35del12 mutations. ERT with rhIDUA was started at 15 months of age (0.58 mg/kg/week) and HSCT was performed at 20 months of age using marrow stem cells from her HLA-identical, non-carrier sibling. At the time of HSCT, she had begun to walk and spoke a few words. She had full engraftment with normalization of plasma IDUA activity; her most recent urine GAG concentration remained slightly elevated (17.4 mg/mmol creatinine; normal <16). At the time of this writing, she is slightly over 4 years of age, slightly developmentally delayed, but making steady progress. She has mild-moderate sensorineural hearing loss, cervical spinal stenosis without spinal cord compression, and continues to have primary enuresis.