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Case Report

Long-term cognitive and somatic outcomes of enzyme replacement therapy in untransplanted Hurler syndrome

Julie B. Eisengart[a,*], Jeanine Jarnes[b], Alia Ahmed[a], Igor Nestrasil[a], Richard Ziegler[a], Kathleen Delaney[c], Elsa Shapiro[a,d], Chester Whitley[a,b]

[a] Department of Pediatrics, University of Minnesota, 420 Delaware Street SE, Minneapolis, MN 55455, USA
[b] College of Pharmacy, University of Minnesota, 420 Delaware Street SE, Minneapolis, MN 55455, USA
[c] BioMarin, 770 Lindaro Street, San Rafael, CA 94901, USA
[d] Shapiro Neuropsychology Consulting, LLC, 820 NW 12th Avenue #304, Portland, OR 97209, USA

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ABSTRACT

Mucopolysaccharidosis type I (MPS I) was added to the Recommended Uniform Screening Panel for newborn screening in 2016, highlighting recognition that early treatment of MPS I is critical to stem progressive, irreversible disease manifestations. Enzyme replacement therapy (ERT) is an approved treatment for all MPS I phenotypes, but because the severe form (MPS IH, Hurler syndrome) involves rapid neurocognitive decline, the impermeable blood-brain-barrier is considered an obstacle for ERT. Instead, hematopoietic cell transplantation (HCT) has long been recommended, as it is believed to be the only therapy that arrests neurocognitive decline. Yet ERT monotherapy has never been compared to HCT, because it is unethically unacceptable to evaluate a therapeutic alternative to one shown to treat Central Nervous System (CNS) disease. An unusual opportunity to address this question is presented with this clinical report of a 16-year-old female with MPS IH treated only with ERT since her diagnosis at age 2. Neurological functioning was stable until cervical spinal cord compression at age 8, hydrocephalus at age 11, and neurocognitive declines beginning at age 10. Somatic disease burden is significant for first degree AV block, restrictive lung disease, bilateral hearing loss, severe corneal clouding, joint pain/limitations requiring mobility assistance, and short stature. This patient's extended survival and prolonged intact neurocognitive functioning depart from the untreated natural history of MPS IH. Disease burden typically controlled by HCT emerged. Although not anticipated to provide benefit for CNS disease, ERT may have provided some amelioration or slowing of neurocognitive deterioration.

1. Introduction

Early treatment is critical for mucopolysaccharidosis type I (MPS I), a progressive disease which the US Secretary of Health and Human Services recommended for addition to the Recommended Uniform Screening Panel for newborn screening in the United States. MPS I is a rare autosomal recessive disorder associated with a deficiency of the lysosomal enzyme α-L-iduronidase, critical for breaking down glycosaminoglycans (GAG) [1,2]. Accumulation of GAG causes progressive, generally irreversible multi-system dysfunction. Early intervention stems accumulating disease pathology [3,4]. An approved treatment for all phenotypes of MPS I is intravenous enzyme replacement therapy (ERT). However, ERT alone is not recommended for the severe form, MPS IH (i.e., Hurler syndrome), which involves central nervous system (CNS) deterioration including neurocognitive decline to the severely to profoundly impaired range before age 4 years [1,3,5,6]. Therapeutic guidelines are based on the presumption that the blood-brain barrier is impermeable to ERT. In contrast, hematopoietic cell transplantation (HCT) arrests CNS deterioration and improves multi-system functioning when performed early in life [3,4,7–10].

Little is known about long-term outcomes of systemic therapies besides HCT for MPS IH. One comparison of HCT, ERT monotherapy, and no treatment showed better survival associated with ERT monotherapy than no systemic treatment, although HCT had the best survival of all [11]. In that study, there was greater cumulative incidence of hydrocephalus and cervical cord compression associated with ERT

Abbreviations: CNS, central nervous system; ERT, Enzyme replacement therapy; HCT, hematopoietic cell transplantation; MPS, Mucopolysaccharidosis; MPS I, Mucopolysaccharidosis Type I; MPS IH, Mucopolysaccharidosis Type IH, Hurler Syndrome; MRI, magnetic resonance imaging

* Corresponding author at: 717 Delaware St. SE, Minneapolis, MN 55414, USA.
E-mail addresses: eisen139@umn.edu (J.B. Eisengart), utzx0002@umn.edu (J. Jarnes), ahmed306@umn.edu (A. Ahmed), nestr007@umn.edu (I. Nestrasil), ziegl002@umn.edu (R. Ziegler), kate.delaney@bmrn.com (K. Delaney), shapi004@umn.edu (E. Shapiro), whitley@umn.edu (C. Whitley).

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monotherapy, compared with HCT. However, no neurocognitive or other somatic outcomes were documented.

The unique opportunity to describe long-term neurocognitive and somatic outcomes of ERT monotherapy in MPS IH is made possible by a female with MPS IH who was diagnosed at age 23 months, when neurocognitively intact, and treated with weekly ERT for the past 14 years. At the time of decision-making about HCT, her intact cognitive functioning and FDA approval of ERT for MPS I, alongside the risks of HCT-related morbidity and mortality, were factors that led the family to choose ERT monotherapy. While this patient was part of the study involving select clinical outcomes previously described [11], she is the only patient with comprehensive neurocognitive and somatic information spanning more than a decade.

2. Patient and methods

2.1. Patient data

This patient's MPS IH was confirmed with genotyping (p.Q70X/p.Q70X). Weekly intravenous ERT was started at age 27 months, at the FDA approved dose of 0.58 mg/kg/week. At 4 years old, her dose was increased to 1 mg/kg/week due to fatigue and facial dysmorphism, with good response. She has been maintained on this dose, and is now 16 years old.

2.2. Methods

Longitudinal medical data were reviewed from multi-disciplinary visits occurring at least annually since age 23 months. She was also seen yearly for 5 years starting at age 8 within a longitudinal study of MPS (NIH U54NS065768), involving annual neurocognitive evaluations and brain MRIs, for which methods have been previously described [3]. For MRI analysis, ventricular volume was computed from automated segmentation of cerebrospinal fluid (CSF) with FreeSurfer Analysis Suite [12], and was defined as a sum of the left and right lateral ventricles along with third and fourth ventricles. Medical data review and the longitudinal study of MPS were both prospectively reviewed and approved by the University of Minnesota IRB.

3. Results

3.1. Neurologic

3.1.1. Neurocognitive

Neurocognitive evaluation was completed annually for 10 years (Fig. 1). Descriptive ranges for scores on neurocognitive tests were defined according to standard clinical practice at the University of Minnesota, as follows: within 1 SD of the population mean (average), −1 SD to −2 SD (below average), and less than or equal to −2 SD (impaired). This patient consistently performed in the average range on verbal and nonverbal IQ tests through age 9 (7 years of treatment). At age 10 her nonverbal IQ scores declined by 20 points to the impaired range, coincident with worsening vision. This decline resulted in a below average total IQ. At age 11 her vision acutely deteriorated to blindness, due to hydrocephalus. Shunting for hydrocephalus yielded return of vision, yet nonverbal cognitive impairment persisted. At age 11 verbal IQ fell below average with no change in nonverbal IQ. At most recent neurocognitive assessment (age 12), verbal and nonverbal IQs continued to decline but were still within their same qualitative ranges of below average and impaired, respectively, representing slowed skill acquisition, rather than actual skill loss. School special education records and correspondence with the parent indicated she attends school full time in the expected grade level for age. Academic records indicated that during 9th grade, reading comprehension was at a 5th grade level. Reading is facilitated with inversion of colors (black background with white text) and audio books.

3.1.2. Hydrocephalus

Decreasing vision led to the diagnosis of communicating hydrocephalus when the patient was 11. Workup included neuro-ophthalmological evaluation, brain MRI and lumbar puncture, revealing an opening pressure of 54 cm of water. There was evidence of optic nerve damage on dilated funduscopic exam and she underwent placement of a ventriculoperitoneal (VP) shunt.

Ventricular CSF volume was measured at four yearly time points and showed a 326% increase in volume over a 34-month period: 100 mL, 159 mL, 249 mL, 325 mL. At the final time point, ventricular CSF accounted for 21% of total brain volume, compared to 8% at baseline and < 1% in unaffected age-matched controls.

3.1.3. Spinal cord compression

At age 8 problems with gait and progressive poor coordination in the upper and lower extremities were caused by cervical spine compression. A C1 laminectomy with open door laminoplasty from C2 through C7 improved symptoms. At age 12 she had mild but consistent progression of pain of her right lower extremity and increased dyscoordination of her lower extremities. MRI showed interval increase in soft tissue along the posterior aspect of the odontoid process with resulting narrowing of the cervical spine. The anterior-posterior dimension of the spinal canal measured about 7 mm in diameter at age 12, reduced from nearly 10 mm at age 9. Craniocervical decompression as well as fusion of the cervical spine were tried. Since, this patient has excellent use of her arms but requires physical and occupational therapies for lower extremity strength. She uses a walker at home but otherwise uses a scooter for mobility.

3.1.4. Carpal tunnel

Carpal tunnel surgery and trigger release to fingers bilaterally occurred at age 3. Since that time there are no sensory disturbances or pain in her hands.

3.2. Cardiac

At age 7 the patient developed first-degree AV block. At most recent checkup (age 15) mild valvular involvement and good ventricular function were noted.

3.3. Pulmonary

This patient has restrictive lung disease, although she is compensating well, without restrictions in activity. Following her spinal surgery at age 12, she required intubation for 4 weeks with concurrent steroid therapy to reduce airway inflammation. She continued on an oral steroid taper for 1 month after hospital discharge and also required 1 l of oxygen by nasal canula at night. She began having recurrent episodes of respiratory infections which presumed to be caused by pneumocystis pneumonia (PCP) based on medication response. Further testing showed low neutrophil counts, IgG, and natural killer cell count. She received IVIG for 1 year, with resolution of recurrent respiratory infections.

3.3.1. Sleep apnea

At age 15 a chest X-ray showed signs of hyperaeration, suggestive of air trapping, prompting a sleep evaluation that indicated severe obstructive sleep apnea and hypoventilation with significant hypoxemia, as well as sleep fragmentation and elevated periodic limb activity with associated arousals. A bilevel PAP was prescribed and successfully instituted, which allowed discontinuation of oxygen therapy during sleeping hours.

3.4. Orthopedic

Shortening of bones and short stature typical of MPS IH are present,