



Case Report

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



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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

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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,

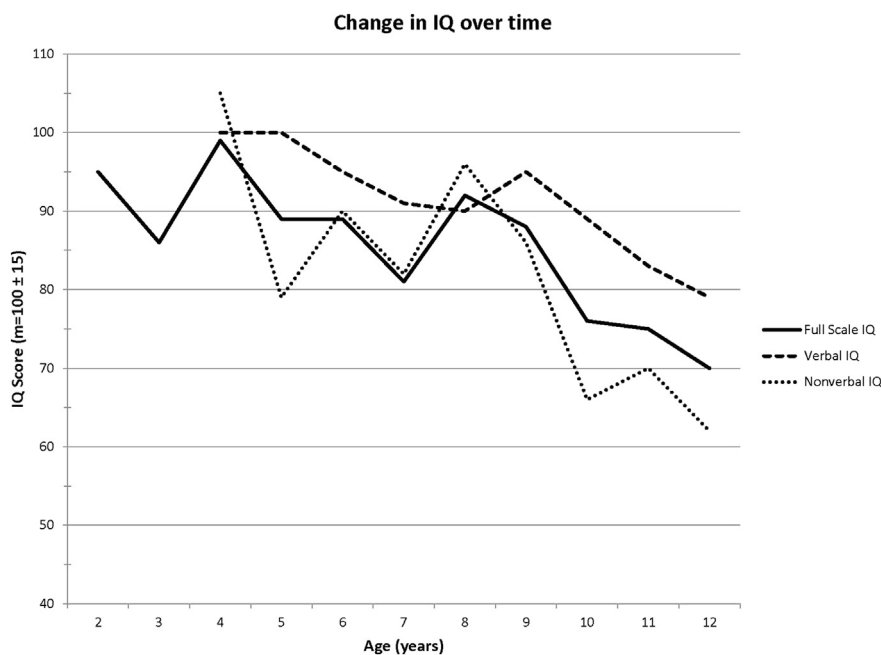


Fig. 1. Downward trend of IQ scores over time. This patient's IQ showed age-typical mild variability when she was a young child and stabilized to the broad average range as she aged. Her IQs began to decline when she started experiencing vision loss at 10 years old, followed by hydrocephalus at age 11. After shunting and return of vision, her IQ did not rebound the next year.

with height consistently measuring at the 0 percentile based on CDC 2–20 years stature-for-age data. Orthopedic exam is positive for kyphoscoliosis, contractures of hands, elbows, shoulders, knees, and ankles. This patient has good range of motion in knees and elbows, while ankles, shoulders, wrists, and fingers have marked limitations. Pain is associated with joint contractures. A right foot fracture at age 15 was treated with a boot for 4 weeks, after which persistent heel pain extending into the back of her leg was noted. She is seen by a physical therapist at least weekly.

3.5. Sensory

3.5.1. Vision

Corneal clouding progressed from mild to severe by age 15. She currently has mild glaucoma with ocular hypertension and mild retinopathy. Loss of vision bilaterally secondary to hydrocephalus was recovered after shunting.

3.5.2. Hearing

At age 11 audiometry showed left moderate to severe sensorineural hearing loss and right profound mixed hearing loss. Multiple placements of bilateral tympanostomy tubes have occurred. A sixth placement was attempted when the patient was 10 but only the left tube was replaced successfully. Other attempts on her right side were aborted later that year due to bleeding, external auditory canal mass, and large vein. At most recent follow up (age 15), an ear tube replacement on the left was successful. Almost total hearing loss was noted in the right ear.

3.6. Endocrine

The patient has had ongoing daily pain and stiffness not alleviated by ERT. She had no improvement in pain or stiffness with pentosan polysulfate sodium treatment. Endocrine hormone insufficiencies are uncommon in MPS I not treated with HCT. There are no concerns in this area.

3.7. Laboratory

Pre-treatment total urine GAG level was 7.74-fold increase above the upper limit of normal (i.e., 96 mg/mmol Cr, using 1,9-dimethylmethylene blue method, with normal reference range being

0–12.4 mg/mmol Cr). In response to ERT, the patient's urine GAG levels were reduced by 62% and have continued stable at approximately 3-fold the upper limit of normal. Anti-ERT antibody levels have been obtained periodically. Anti-ERT antibodies have increased from a titer of 12,800 after 7 years of ERT up to a titer of 25,600 after 13 years of ERT, but have had no apparent impact on the efficacy of ERT. There is no history of infusion reactions.

4. Discussion

This clinical report is a comprehensive examination of the longitudinal course of Hurler syndrome treated with ERT monotherapy, initiated early in life before significant signs of disease progression or CNS pathology. Consistent with other findings [11], this study suggests that very early ERT alters the natural history of MPS IH by extending survival. Further, neurocognitive decline deviated from the untreated natural history, as it occurred later in life and is less severe.

ERT in all phenotypes of MPS I results in reductions in hepatosplenomegaly, urinary glycosaminoglycan excretion, and sleep apnea, as well as improved growth, physical endurance, and joint range of motion [13,14]. However, ERT is not a cure, as established organ damage cannot be reversed [15]. Earlier initiation of ERT in attenuated MPS I appears to delay or reduce disease complications [16–18]. It is believed that ERT at approved doses cannot appreciably cross the blood-brain barrier to treat the CNS pathology of MPS IH. Animal models have enabled dosing manipulation: There was a substantial CNS response in the murine model of Hurler syndrome when mice were treated at 20-fold the standard ERT dose [19]. In humans, HCT is the only approved therapy shown to arrest CNS disease when performed early (see [20] for a review). It has also been shown to result in greater metabolic correction than ERT as seen by substrate reduction [15], and it is associated with better survival than ERT [11]. Nevertheless, patients who have received HCT generally function below the age-typical range neurocognitively, and further, residual disease burden is evident in the skeletal and cardiac systems, even in patients who are fully engrafted [3,4,8,9].

Does this clinical report reveal the expected benefits of ERT? Yes, as this patient has reduced organomegaly. Does she have disease burden that is known to persist in other patients, even patients who have received HCT? Yes, she experiences short stature and orthopedic problems, AV block, overnight hypoxia, hearing loss, pain and stiffness,

and mobility reduction, which have all been shown in long-term follow-up of patients with MPS IH who underwent HCT (e.g., [4,8,21]). She also has spinal cord compression. To date, findings are equivocal regarding the success of HCT in preventing this symptom [3,22].

Symptoms of MPS IH typically controlled by HCT have occurred in this patient, including hydrocephalus, pulmonary problems, and severe corneal clouding. This patient's neurocognitive course is not consistent with outcomes associated with the untreated natural history nor with HCT, including the combined therapy of HCT and ERT [3,4,9,23,24]. Her neurocognitive functioning was age-typical and stable until she developed hydrocephalus, which is well known to affect neurocognitive functioning even in patients without MPS, and is likely a major factor in her neurocognitive decline. Her decline has appeared not to continue at the same downward pace since her hydrocephalus was treated. Her unusual cognitive trajectory could be interpreted within the context of ERT, which has been associated with more favorable cognitive outcomes when combined with HCT, versus HCT alone [23].

Higher doses of ERT (i.e., 1 mg/kg/week instead of the conventional 0.58 mg/kg/week) may possibly have played a role in slowing this patient's disease progression. Improvement in her endurance at the higher dose versus the lower dose, by parent report, raises the possibility that the higher ERT dosing may have contributed to improvements in the patient's clinical status. Further, this patient's regular follow-up schedule of specialist appointments has enabled rapid addressing of her physical problems, which likely has resulted in better overall outcomes.

5. Conclusions

This comprehensive examination of long-term outcomes of ERT in MPS IH suggests that ERT initiated early in life alters natural history, in line with findings for attenuated MPS I [16–18]. This patient's continued survival is consistent with previous findings of extended survival in patients with the same treatment course [11]. Neurologic and somatic symptoms that are typically controlled by HCT did emerge and may have implications for quality of life. This patient's outcomes raise the possibility that ERT, although not anticipated to provide benefit for CNS disease in MPS IH, may have provided some amelioration or slowing of neurocognitive decline. These findings are important as newborn screening enables earliest intervention in the United States and the array of therapeutic opportunity grows. Optimal dosing of ERT requires further study to determine if additional benefits such as slowing CNS disease progression may be realized with higher dosing.

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Disclosures

Julie Eisengart has received honoraria from Sanofi Genzyme and has done consulting work for Shapiro Neuropsychology Consulting, LLC; Kathleen Delaney is an employee of BioMarin; Elsa Shapiro is a Partner in Shapiro Neuropsychology Consulting, LLC, and Chester B. Whitley has received consulting fees and research support from BioMarin and Sanofi Genzyme. The other authors have no conflicts of

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