

# Intrathecal Enzyme Replacement Therapy Reverses Cognitive Decline in Mucopolysaccharidosis type I

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Mucopolysaccharidosis type I (MPS I) is an inherited lysosomal storage disease that seriously affects the brain. Severity of neurocognitive symptoms in attenuated MPS subtype (MPS IA) broadly varies partially, due to restricted permeability of blood-brain barrier (BBB) which limits treatment effects of intravenously applied  $\alpha$ -L-iduronidase (rhIDU) enzyme. Intrathecal (IT) rhIDU application as a possible solution to circumvent BBB improved brain outcomes in canine models; therefore, our study quantifies effects of IT rhIDU on brain structure and function in an MPS IA patient with previous progressive cognitive decline. Neuropsychological testing and MRIs were performed twice prior (baseline, at 1 year) and twice after initiating IT rhIDU (at 2nd and 3rd years). The difference between pre- and post-treatment means was evaluated as a percentage of the change. Neurocognitive performance improved particularly in memory tests and resulted in improved school performance after IT rhIDU treatment. White matter (WM) integrity improved together with an increase of WM and corpus callosum volumes. Hippocampal and gray matter volume decreased which may either parallel reduction of glycosaminoglycan storage or reflect typical longitudinal brain changes in early adulthood. In conclusion, our outcomes suggest neurological benefits of IT rhIDU compared to the intravenous administration on brain structure and function in a single MPS IA patient.

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**Key words:** mucopolysaccharidosis; intrathecal administration; enzyme replacement therapy; neuropsychology; magnetic resonance imaging; diffusion tensor imaging; brain; blood-brain barrier

## INTRODUCTION

Mucopolysaccharidosis I (MPS I) is a rare genetic condition caused by the deficiency of the  $\alpha$ -L-iduronidase enzyme, which results in

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storage of glycosaminoglycans (GAGs) [Muenzer et al., 2009]. While MPS severely affects brain structure, symptoms range from the most severe (Hurler syndrome) to the attenuated (Hurler-Scheie and Scheie) forms [Muenzer et al., 2009]. Untreated Hurler patients exhibit cognitive decline and morphological brain abnormalities, while neuropsychological deficits in attenuated forms are variable [Shapiro et al., 2015]. For severe patients, hematopoietic stem cell transplantation (HSCT) is the current standard of care that stabilizes cognitive functions [Peters et al., 1996]. In attenuated forms, enzyme replacement therapy (ERT) utilizing recombinant human  $\alpha$ -L-iduronidase (rhIDU), improves somatic symptoms and quality of life [Kakkis et al., 2001]. ERT administered intravenously cannot penetrate the intact blood-brain barrier, thereby limiting the potential benefits on brain structure and function [Kakkis et al., 2001]. However, intrathecal (IT) administration of the enzyme directly into the spinal canal improved lysosomal storage and neuropathology in canine models [Dickson and Chen, 2011; Vite et al., 2013]. The objective of this study was to determine whether IT administration of rhIDU in a Hurler-Scheie patient with progressive cognitive decline could stabilize or reverse the cognitive deficits and impact structural brain defects.

## MATERIALS AND METHODS

### Human Subjects

A 23-year old male Hurler-Scheie patient with mild A327P/G265R; missense/missense mutation, who had a measurable cognitive decline and progressive impairment in ability to perform in school over 18 months was enrolled on an Institutional Review Board (IRB), approved at University of Texas Southwestern Medical Center. He had been treated with intravenous rhIDU for 13 years before IT rhIDU and had not undergone HSCT. The patient was enrolled concurrently in an IRB approved non-interventional longitudinal study of brain structure and function in MPS (NCT01870375) at the University of Minnesota.

### Treatment and Clinical Evaluation

The patient was treated with 3 cc of rhIDU (approximately 1.74 mg) diluted with 6 cc of Elliotts B<sup>®</sup> artificial cerebrospinal fluid (CSF) solution, for a total IT injection of 9 cc via a fluoroscopy-guided lumbar puncture on day 0, after baseline assessments and repeated monthly for 3 months and every 3 months, thereafter for a total of 24 months.

The brain magnetic resonance imaging (MRI) acquired on 3T Siemens Trio was analyzed for volumetric data using T1-weighted images and for white matter (WM) integrity using diffusion tensor imaging (DTI) [Alexander et al., 2007] (for details see supplement).

Neuropsychological testing and MRIs were performed twice prior to the IT administration (baseline, at 1 year) and at 2nd and 3rd years after initiating IT rhIDU. Neurocognitive deficit was quantified as a score of one standard deviation (SD), below the mean on at least one domain of neuropsychological function. The difference between pre- and post-treatment means was evaluated as a percentage of the change. Neuropsychological battery included tests of intelligence, attention, adaptive skills,

and visual and verbal memory. All psychological scores are reported as standard scores, with a mean of 100 and a standard deviation of 15 from published normative data. Details of the tests can be found in Table I.

Monitoring of adverse events (AEs), CSF laboratory, and clinical evaluations assessed the safety of IT rhIDU [Felice et al., 2011].

## RESULTS

### Magnetic Resonance Imaging

Brain MRI revealed an increase in the mean WM and corpus callosum (CC) volumes post-IT rhIDU (Table I). The mean gray matter (GM) volume and the mean left and right hippocampal volumes decreased after IT treatment. Fractional anisotropy (FA) and axial diffusivity (AD) in whole brain WM increased, whereas mean diffusivity (MD) and radial diffusivity (RD) decreased.

### Neurocognitive Tests

At baseline, the patient demonstrated significant visual and verbal encoding memory deficits, and a lower than average score on the measure of adaptive behavior. All other tests were in the average range.

The mean IQ scores improved in all subtests. Attention scores increased in impulsivity and variability, and decreased in vigilance and reaction time post-IT rhIDU.

Visual memory increased in both total and delayed recall scores. Importantly, mean verbal memory scores significantly increased for encoding (total number of words recalled after each of three presentations of a list of words) and for delayed recall score (number of words recalled after a delay of 20 min) post-IT rhIDU. The Logical Memory measure (repetition of verbal material in a context) improved and the mean adaptive scores increased in the domains of Socialization, Communication, and Daily Living Skills as well as on the Composite score. Consequently, the patient has marked improvement in ability to read, remember, and perform tasks in school.

### Safety Measures

The patient tolerated IT application with minimal adverse events. Occasional mild headache, moderate lumbar stiffness, and one spinal headache spontaneously resolved without intervention within 24 hr.

## DISCUSSION

A 23-year-old male with Hurler-Scheie syndrome, showed stable or improved neurocognitive outcomes after 24 months of IT rhIDU, while experiencing no serious adverse events. The patient showed the greatest improvement in his ability to encode verbal stimuli, moving from significantly impaired to the average level. This was accompanied by a significant improvement in adaptive behavior and an improvement to an above average level, in his ability to remember verbal material in a context. Nonverbal memory, both encoding and recall increased although those scores remained

TABLE I. Summary of the Neurocognitive and Structural Brain Outcomes

Measurement	Pre-IT rhIDU			Post-IT rhIDU			Difference (%)	
	BaseL	1 year	Mean	2 year	3 year	Mean	%	Ch
IQ								
VIQ	99	107	103	106	108	107	3.7	Im
PIQ	93	100	97	97	110	104	6.7	Im
FSIQ	96	104	100	106	110	108	7.4	Im
TOVA								
Omissions	101	108	104,5	101	101	101	-3.5	Wo
Commissions	106	117	112	117	119	118	5.1	Im
Reaction time	105	110	107,5	114	93	103,5	-3.9	Wo
Variability	98	100	99	116	102	109	9.2	Im
BVMt-R								
Total	55	68	62	55	79	67	8.2	Im
Delayed	55	73	64	64	83	74	12.9	Im
HvLT-R								
Total	55	59	57	85	94	90	36.3	Im
Delayed	56	37	47	85	105	95	51.1	Im
WMS-IV								
Logical memory	105	105	105	115	115	115	8.7	Im
VABS-II								
Composite score	83	89	86	103	98	101	14.4	Im
Daily living score	90	100	95	100	96	98	3.1	Im
Socialization	82	78	80	111	101	106	24.5	Im
Communication score	90	100	95	104	104	104	8.7	Im
Volumes								
White matter (cm <sup>3</sup> )	515.99	522.80	519.40	527.31	539.37	533.34	2.6	Im*
Gray matter (cm <sup>3</sup> )	815.16	808.64	811.90	800.05	773.60	786.83	-3.2	Im*
CC (cm <sup>3</sup> )	4.30	4.22	4.26	4.34	4.36	4.35	2.1	Im
Hippocampus (cm <sup>3</sup> )								
Left	2.45	2.21	2.33	2.15	2.22	2.19	-6.3	Im**
Right	2.69	2.42	2.55	2.28	2.28	2.28	-11.9	Im**
DTI								
FA	0.38	0.38	0.381	0.37	0.39	0.382	0.2	Im
MD (mm <sup>2</sup> /s) [10 <sup>-4</sup> ]	7.88	7.74	7.81	7.88	7.70	7.79	-0.3	Im
RD (mm <sup>2</sup> /s) [10 <sup>-4</sup> ]	6.28	6.16	6.22	6.21	6.10	6.16	-1.1	Im
AD (mm <sup>2</sup> /s) [10 <sup>-4</sup> ]	11.09	10.95	11.02	11.20	11.09	11.15	1.1	Im

IT, Intrathecal; rhIDU,  $\alpha$ -L-iduronidase; CC, corpus callosum; DTI, Diffusion Tensor Imaging; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity; Ch, Character of change; Im, Improvement; Wo, worsening.

Tests:

WASI: Wechsler Abbreviated Scale of Intelligence; IQ: intelligence quotient.

TOVA: Test of Variables of Attention; omission errors measures vigilance, errors of commission measures impulsivity.

BVMt-R: Brief Visuospatial Memory Test-Revised.

HvLT-R: Hopkins Verbal Learning Test-Revised.

WMS-IV: Wechsler Memory Scale-Fourth Edition (Logical Memory only).

VABS-II: Vineland Adaptive Behavior Scale-Second Edition.

\*Patterns of volumetric changes are in line with typical brain variations in early adulthood, although the magnitude is higher (0.39% decrease in GM and hippocampal volume, 0.23% increase in WM volume per year in healthy individuals in the same age).

\*\*Changes are likely associated with decrease of GAG as reported in animal model.

below the average range. A baseline of average IQ and attention performance also somewhat improved.

In line with meta-analysis outcomes, hippocampal volume decreases may parallel the improvement in learning and memory [Van Petten, 2004] and may reflect aging [Tisserand et al., 2000] together with a reduction in GAGs storage. Indeed, canine MPS models proved that IT rhIDU normalizes hippocampal GAGs levels [Dierenfeld et al., 2010]. The increase of CC volume aligns with the

effects of IT rhIDU in MPS I dogs [Vite et al., 2013]. IT-ERT treatment may facilitate typical brain volumetric changes in early adulthood [Good et al., 2001] since, it leads to almost 10 times higher effects compared to 0.39% average decrease of hippocampal and GM volume and 0.23% increase in WM volume per year in healthy individuals younger than 34 years [Liu et al., 2003]. Similarly to attenuated MPS II [Yund et al., 2015] an improvement of WM and CC volume may be related to improved attention.

Lower RD values suggest a more intact myelin sheath, accompanied by improved axonal integrity measured as higher AD [Alexander et al., 2007] post-IT. Lower MD and higher FA mirrored these changes. DTI measures in healthy individuals follow a curvilinear longitudinal pattern during lifespan with a relative plateau in early adulthood, although frontal cognitive connections (e.g., cingulum bundle, uncinate fascicle) are continuously maturing around 25 years of age [Yap et al., 2013]. Hence, DTI outcomes indicate an overall improvement of WM integrity and/or continuation of development in frontal fiber bundles post-IT rhIDU.

## CONCLUSION

In this single case study of an attenuated MPS I patient, IT rhIDU was associated with improvements or maintenance in memory, attention, and learning functions. The related changes in brain microstructure suggest that IT rhIDU may have a significant impact on neurocognitive function in patients, who have progressive neurocognitive decline resulting from lack of CNS penetration after intravenous administration.

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## REFERENCES

- Alexander AL, Lee JE, Lazar M, Field AS. 2007. Diffusion tensor imaging of the brain. *Neurotherapeutics* 4:316–329.
- Dickson PI, Chen AH. 2011. Intrathecal enzyme replacement therapy for mucopolysaccharidosis I: Translating success in animal models to patients. *Curr Pharm Biotechnol* 12:946–955.
- Dierenfeld AD, McEntee MF, Vogler CA, Vite CH, Chen AH, Passage M, Le S, Shah S, Jens JK, Snella EM, Kline KL, Parkes JD, Ware WA, Moran LE, Fales-Williams AJ, Wengert JA, Whitley RD, Betts DM, Boal AM, Riedesel EA, Gross W, Ellinwood NM, Dickson PI. 2010. Replacing the enzyme alpha-L-iduronidase at birth ameliorates symptoms in the brain and periphery of dogs with mucopolysaccharidosis type I. *Sci Transl Med* 2:60ra89.
- Felice BR, Wright TL, Boyd RB, Butt MT, Pfeifer RW, Pan J, Ruiz JA, Heartlein MW, Calias P. 2011. Safety evaluation of chronic intrathecal administration of idursulfase-IT in cynomolgus monkeys. *Toxicol Pathol* 39:879–892.
- Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14:21–36.
- Kakkis ED, Muenzer J, Tiller GE, Waber L, Belmont J, Passage M, Izykowski B, Phillips J, Doroshov R, Walot I, Hoft R, Neufeld EF. 2001. Enzyme-replacement therapy in mucopolysaccharidosis I. *N Engl J Med* 344:182–188.
- Liu RSN, Lemieux L, Bell GS, Sisodiya SM, Shorvon SD, Sander JWAS, Duncan JS. 2003. A longitudinal study of brain morphometrics using quantitative magnetic resonance imaging and difference image analysis. *Neuroimage* 20:22–33.
- Muenzer J, Wraith JE, Clarke LA. 2009. International consensus panel on management and treatment of mucopolysaccharidosis I. *Pediatrics* 123: 19–29.
- Peters C, Balthazor M, Shapiro EG, King RJ, Kollman C, Hegland JD, Henslee-Downey J, Trigg ME, Cowan MJ, Sanders J, Bunin N, Weinstein H, Lenarsky C, Falk P, Harris R, Bowen T, Williams TE, Grayson GH, Warkentin P, Sender L, Cool VA, Crittenden M, Packman S, Kaplan P, Lockman LA, Anderson J, Krivit W, Dusenbery K, Wagner J. 1996. Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. *Blood* 87:4894–4902.
- Shapiro EG, Nestrail I, Rudser K, Delaney K, Kovac V, Ahmed A, Yund B, Orchard PJ, Eisengart J, Niklason GR, Raiman J, Mamak E, Cowan MJ, Bailey-Olson M, Harmatz P, Shankar SP, Cagle S, Ali N, Steiner RD, Wozniak J, Lim KO, Whitley CB. 2015. Neurocognition across the spectrum of mucopolysaccharidosis type I: Age, severity, and treatment. *Mol Genet Metab* 116:61–68.
- Tisserand DJ, Visser PJ, Van Boxtel MPJ, Jolles J. 2000. The relation between global and limbic brain volumes on MRI and cognitive performance in healthy individuals across the age range. *Neurobiol Aging* 21:569–576.
- Van Petten C. 2004. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: Review and meta-analysis. *Neuropsychologia* 42:1394–1413.
- Vite CH, Nestrail I, Mlikotic A, Jens JK, Snella EM, Gross W, Shapiro EG, Kovac V, Provenzale JM, Chen S, Le SQ, Kan S, Banakar S, Wang RY, Haskins ME, Ellinwood NM, Dickson PI. 2013. Features of brain MRI in dogs with treated and untreated mucopolysaccharidosis type I. *Comp Med* 63:163–173.
- Yap QJ, Teh I, Fusar-Poli P, Sum MY, Kuswanto C, Sim K. 2013. Tracking cerebral white matter changes across the lifespan: Insights from diffusion tensor imaging studies. *J Neural Transm* 120: 1369–1395.
- Yund B, Rudser K, Ahmed A, Kovac V, Nestrail I, Raiman J, Mamak E, Harmatz P, Steiner R, Lau H, Vekaria P, Wozniak JR, Lim KO, Delaney K, Whitley C, Shapiro EG. 2015. Cognitive, medical, and neuroimaging characteristics of attenuated mucopolysaccharidosis type II. *Mol Genet Metab* 114:170–177.

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