

Longitudinal neurocognitive outcome in an adolescent with Hurler-Scheie syndrome

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Abstract: An adolescent with Hurler-Scheie syndrome is reported. This now 15 year-old-young woman was initially diagnosed at age 4. She was assessed for neurocognitive functioning at ages 5, 13, and 15 years. Results show a significant decline in intellectual functioning from the superior range to the average range from age 5 to age 13, and then no change from age 13 to age 15. The relationship between Hurler-Scheie syndrome, premorbid intellectual functioning, and cognitive-behavioral interventions are discussed in light of the longitudinal neurocognitive effects of this disease.

Keywords: Hurler-Scheie syndrome, adolescent, neurocognitive function

Introduction

The mucopolysaccharidoses (MPS) are a family of genetic disorders characterized by changes in an individual's ability to metabolize mucopolysaccharides, which are complex sugar molecules found in the connective tissue, mucosal fluids, synovial fluid, and other cells throughout the body. There are six types of MPS, with some types having several subtypes. According to Brown (1999), epidemiological data are problematic to report, but range from 1 in 100 000 live births to 1 in 600 000 live births. This dysfunction in metabolism may result in a variety of distinct physical features, such as short stature, contracture of joints, claw-like hands, abnormal spine curvature, and hydrocephalus (Neufeld and Muenzer 1995). Treatment options vary, but hematopoietic cell transplantation seems to offer the best long-term quality of life improvement and decreased mortality and morbidity options for children with some of the more severe forms of MPS (Grewal et al 2002).

One subtype of MPS is MPS I, which includes Hurler, Scheie, and Hurler-Scheie syndromes. Each of these disorders within MPS I is caused by a deficiency of alpha-L-iduronidase. Within MPS I, Hurler syndrome is generally associated with more severe features and poorer prognosis than either Scheie or Hurler-Scheie syndromes (Brown 1999). In most cases of Hurler syndrome, motor skills are limited by age 18 months, and developmental regression occurs, including progressive loss of neurocognitive functioning, resulting in mental retardation. With Hurler-Scheie syndrome, these declines usually appear between 3 and 8 years of age, with milder neurocognitive losses and a low risk for early mortality. These neurocognitive losses typically include progressive dementia resulting from hydrocephalus and increasing deposits of nonmetabolized mucopolysaccharides (Shapiro et al 1995). Language and memory deficits after a period of initial developmental slowing have been associated with the more severe forms of MPS I (Guffon et al 1998).

While neurocognitive deficits have been associated with MPS, to date there are few neurocognitive reports of children with this disorder and no longitudinal studies, resulting in scant knowledge regarding appropriate assessment and intervention (Brown 1999). Many studies report cross-sectional assessments of these children at different stages. In this case report, we have the opportunity to follow a young lady

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with Hurler-Scheie syndrome over the course of 10 years, documenting the quantity and quality of neurocognitive effects associated with this disease. This represents a rare chance to longitudinally track the effects of Hurler-Scheie in a young person and allows recommendations to be made to health care professionals regarding potential neurocognitive and psychological care for children with this disorder.

Researchers are currently engaging in novel therapies designed to reduce and perhaps reverse the effects of Hurler-Scheie. However, while these therapies may have a beneficial effect on orthopedic, skeletal, or ophthalmic problems, their effect on neurocognitive functioning is not clearly understood. Thus, we are in a position to begin documenting both the physiological and neurocognitive effects of these new treatments. The focus of this case report is to describe long-term neurocognitive changes in a young female with Hurler-Scheie syndrome that was treated using enzyme replacement therapy. To our knowledge, this is the first longitudinal case report of a patient receiving enzyme replacement therapy for Hurler-Scheie syndrome.

Case report

The following information was collected with the approval of the Institutional Review Board at the University of Mississippi Medical Center. Written consent was obtained from both the patient and her parent. We report the case of a now 15-year-old female diagnosed with MPS-I, specifically Hurler-Scheie syndrome, Alpha (not her real name). Alpha's mother gave consent for her child to serve as a subject in this investigation, and Alpha gave assent. Alpha was the product of a normal pregnancy, labor, and delivery. Family history is negative for known neuromuscular or metabolic disorders. Her parents are both college-educated professionals. Her mother reported Alpha grew well at first, but then seemed to "slow down." Her mother also noted Alpha could not raise her arms over her head, even as an infant. At age 3.5 years, Alpha complained of wrist pain, and was seen by her primary care physician. Alpha began taking gymnastics class as part of her 4-year-old preschool; her instructor noted that Alpha could not touch her toes or raise her arms.

Alpha was then referred to a local orthopedic clinic and x-rays were obtained. According to Alpha's mother, the clinic noted "something wrong" on the x-ray films, and referred Alpha to a pediatric orthopedic surgeon for further evaluation. The surgeon noted that Alpha had no scoliosis.

Alpha could not actively abduct her shoulders beyond 90 degrees and passive abduction was limited to 130 degrees. She was noted to have good finger function and grip, and a full range of motion in her neck, hips, knees, ankles, and elbows, with no appreciable organomegaly. The initial diagnosis considered was arthrogryposis. However, after reviewing the x-rays and noting atypical features such as broad ribs with some notching at the medial metaphyseal ends, and smaller than usual femoral heads bilaterally, the orthopedic surgeon suspected Alpha had Scheie syndrome, one of the MPS I syndromes. Alpha was referred to a geneticist to conduct urine and blood tests and was diagnosed with Hurler-Scheie syndrome.

By age 8, Alpha remained a very happy, bright young lady who was active in theatre camp and swimming (she used her own, special technique according to her mother). She could actively abduct her shoulders 80 degrees and had about 50% range of motion in her neck. She was wearing glasses, was an avid reader, and was doing very well in school.

By age 10 in 1999, Alpha was 50 inches (124 cm) tall and weighed 71 pounds (32 kg). She had restricted range of motion in her hips and knees, and was beginning to complain of neck pain.

In 2000, at the age of 12, Alpha was admitted for the placement of a VP shunt secondary to increasing hydrocephalus. She currently maintains this shunt, with no complications. She also began enzyme replacement therapy in 2000 on a pharmaceutical study at the age of 12, as well as outpatient physical therapy to encourage range of motion in her extremities. Her physical condition improved, so that she had better range of motion. Tanner staging was noted as appropriate for her age; in general, Hurler-Scheie and Scheie patients have normal puberty and reproductive abilities. She has strong family support and appropriate expectations for her future.

Her neurocognitive functioning was assessed three times, in June 1994 when she was 5 years 11 months old, in June 2002 when she was 13 years 11 months old, and in July 2003, when she was 15 years old. The initial assessment at age 5–11 was not conducted by the authors, but took place at another location. However, this assessment was done by a licensed clinical psychologist who used age-appropriate, valid measures. Copies of the report from that assessment were reviewed from the patient's medical chart.

Given her young age (5–11) at her initial assessment, the patient was administered the Stanford-Binet Intelligence Scale, Fourth Edition, and the Wide Range Achievement

Table 1 Initial evaluation, age 5–11

Measure	Subtest	Standard score	Percentile	Range
Stanford-Binet M=100, SD=16	Composite (IQ)	121	91	Superior
	Verbal reasoning	112	77	High average
	Abstract-visual reasoning	140	99	Very superior
	Quantitative reasoning	116	84	High average
	Short-term memory	102	55	Average
Wide range achievement test M=100, SD=15	Reading	123	94	Superior
	Spelling	120	91	Superior
	Arithmetic	121	92	Superior

Test, Third Edition (see Table 1). These measures assess for intelligence (IQ) and achievement, respectively. At the time, the patient had just completed kindergarten, had no behavior problems, and was considered by her teachers to be ready for the first grade. Her mother likewise thought the patient was doing well academically, but was concerned that the patient could perhaps have been showing signs of mild forgetfulness. Overall, the scores on these measures range from the average to the highly superior range, as she scored at or above the 90th percentile in most areas. At that time, it was clear that Alpha was functioning in the average to superior range intellectually and academically, and had no significant behavioral or emotional problems.

Alpha's parents were aware of the impressive nature of these findings, but were also aware of the usual course of this disease, including gradual neurocognitive decline. They began both systematic and non-specific interventions designed to challenge Alpha intellectually and stimulate her already significant cognitive abilities. These included summer camps, art classes, and music lessons. Alpha was enrolled in a school that stressed academic excellence, and her mother reported that Alpha did well through the seventh grade. Alpha was home-schooled for the second half of the seventh grade, as she was travelling frequently to receive treatment for her condition. When she began eighth grade back at her same school, her grades began to fall from consistent As up through the seventh grade to Bs and Cs in the eighth grade. This prompted Alpha's parents to seek another neurocognitive evaluation.

At the time of the second assessment, the patient was 13 years and 11 months, and so could complete a more comprehensive neurocognitive battery (see Table 2). This second battery consisted of parts of the Wechsler Intelligence Scale for Children – Third Edition (WISC-III), Woodcock-Johnson Tests of Cognitive Ability – Third Edition (WJ-

III), the Wide Range Assessment of Memory and Learning (WRAML), the California Verbal Learning Test – Children's Version (CVLT-C), the Stroop Color and Word Test, the Rey-Osterrieth Complex Figure Test (ROCF), the Child Behavior Checklist (CBCL-parent report), the Youth Self Report (YSR), the Children's Depression Inventory (CDI), and the Revised Children's Anxiety and Depression Scale (RCADS). This battery is designed to be a comprehensive measure of intelligence, neurocognitive functioning, and behavioral and emotional adjustment. It should be noted that though different batteries of measures were used between neurocognitive assessments, the results from both assessments are comparable. Specifically, overall intelligence quotient (IQ) scores between the Stanford-Binet and the Woodcock-Johnson show good correlation (Sattler 1992).

Results from this second assessment indicate a significant decline in overall abilities from Alpha's initial level of functioning. Her abilities were now within the average range of functioning; however, she again demonstrated no significant behavioral or emotional problems. Alpha's parents began implementing suggested interventions, including after school tutoring and structuring Alpha's study time so that she studied for short blocks of time with frequent breaks. At the time of this report, Alpha's mother described Alpha as doing better in school (generally Bs and Cs, a few As), and continuing to be emotionally and socially well-adjusted.

Alpha completed her third assessment battery approximately one year later at age 15–0. She completed the same battery as the one she completed at age 13–11 (see Table 3). This third assessment demonstrated no further decline in intellectual functioning from the second assessment. As before, no behavioral or emotional difficulties were reported.

Discussion

While declines in neurocognitive functioning are generally expected in children with MPS, this case report of a young lady with Hurler-Scheie demonstrates that declines may proceed at different rates and are likely influenced by premorbid neurocognitive functioning and environmental-behavioral vectors. In other words, Alpha's current level of "average" neurocognitive functioning is probably the result of impressive capabilities prior to the onset of Hurler's syndrome as well as the degree of intervention and cognitive expectations that characterize her family system. The idea of cognitive reserve as a protective factor in individuals who have some sort of neurological insult has been assumed in children with traumatic brain injury and brain tumors. Thus, it could be that since Alpha had such a high premorbid level of functioning, she had more to "spare" during the course of her illness and treatment (Taylor 2004). It should be noted that many children with Hurler-Scheie show some degree of cognitive sparing, in comparison with other types of MPS. However, this sparing is remarkable for its robustness. Also, biological factors should be considered as influencing these

findings. It should be noted that Alpha has been diagnosed with a milder form of MPS, Hurler-Scheie, and that this subtype of MPS has been shown to involve relative neurocognitive sparing (Brown 1999). However, this report is the first of its kind to our knowledge to document longitudinal changes in a youngster.

The issue of Alpha's current level of neurocognitive functioning cannot be fully addressed in this report. Her initial decline is undoubtedly related to her diagnosis of Hurler-Scheie syndrome. However, the amount of decline and conversely the degree of neurocognitive sparing attributable to her premorbid functioning and behavioral interventions by her parents is indeterminable. The differences in her test performance may be attributable to regression to the mean, a common result of multiple assessments conducted on a single individual. Consequently, we cannot estimate the amount of variance accounted for by Alpha's premorbid intellectual capabilities, Hurler-Scheie syndrome, and her parents' level of cognitive and intellectual interventions. It should also be noted that the measured decline in IQ might be related to progressive motor

Table 2 Second evaluation, age 13-11

Measure	Subtest	Standard score	Percentile	Range
WJ-III M=100, SD=15	General intellectual ability (IQ)	100	50	Average
	Verbal ability	104	61	Average
	Thinking ability	100	49	Average
	Cognitive efficiency	95	37	Average
	Phonemic awareness	102	55	Average
	Working memory	97	42	Average
WISC-III M=10, SD=3	Spatial span	13		High average
WRAML M=10, SD=3	Visual learning	7		Low average
CVLT-C M=0.0, SD=1.0	List A trial 1 free recall	0.0		Average
	List A trial 5 free recall	0.5		Average
	List B free recall	-0.5		Average
	Semantic clustering	2.5		Superior
	Serial clustering	-1.0		Low average
	Recognition	0.0		Average
ROCF M=10, SD=3	Copy	12	75	Average
	Immediate recall	13	100	Superior
	Delayed recall	13	100	Superior
Stroop M=100, SD=15	Word score	95		Average
	Color score	91		Average
	Color-word score	100		Average
	Interference	107		Average

Abbreviations: CVLT-C, California Verbal Learning Test – Children's Version; ROCF, Rey-Osterrieth Complex Figure Test; WISC-III, Wechsler Intelligence Scale for Children – Third Edition; WJ-III, Woodcock-Johnson Tests of Cognitive Ability – Third Edition; WRAML, Wide Range Assessment of Memory and Learning.

Table 3 Third evaluation, age 15–0

Measure	Subtest	Standard score	Percentile	Range
WJ-III M=100, SD=15	General intellectual ability (IQ)	101	54	Average
	Verbal ability	98	44	Average
	Thinking ability	98	46	Average
	Cognitive efficiency	108	70	Average
	Phonemic awareness	112	79	Average
	Working memory	100	49	Average
WISC-III M=10, SD=3	Spatial span	13		High average
WRAML M=10, SD=3	Visual learning	6		Low average
CVLT-C M=0.0, SD=1.0	List A trial 1 free recall	1.0		Average
	List A trial 5 free recall	1.0		Average
	List B free recall	0.0		Average
	Semantic clustering	3.0		Superior
	Serial clustering	−1.0		Low average
	Recognition	0.0		Average
ROCF M=10, SD=3	Copy	13	100	Average
	Immediate recall	13	100	Superior
	Delayed recall	12	75	Superior
Stroop M=100, SD=15	Word score	92		Average
	Color score	91		Average
	Color-word score	111		Average
	Interference	117		HighAverage

Abbreviations: CVLT-C, California Verbal Learning Test – Children's Version; ROCF, Rey-Osterrieth Complex Figure Test; WISC-III, Wechsler Intelligence Scale for Children – Third Edition; WJ-III, Woodcock-Johnson Tests of Cognitive Ability – Third Edition; WRAML, Wide Range Assessment of Memory and Learning.

dysfunction, as this might affect some of the subtests on the neurocognitive measures. There are no reports of the possible neurocognitive-sparing or –improving effects of enzyme replacement therapy, which Alpha received. Further research in this area is warranted.

Weaknesses of this case report include the use of different measures of intelligence and neurocognitive functioning. However, all measures used to assess this patient are well-established, well-validated measures, and hence should be interpreted as adequately reflecting her level of neurocognitive functioning at the time they were administered.

Conclusion

This case represents a unique opportunity to study a genetic disorder with neurocognitive effects, in the light of apparently strong biological and environmental protective factors. Children with Hurler-Scheie syndrome should be followed regularly with neurocognitive assessments in order both to document expected intellectual declines and to target areas for cognitive and behavioral interventions that might slow the decline associated with this disease. The strong

behavioral and environmental support that Alpha received from her parents cannot be discounted. Alpha's parents proactively began working with her in light of her diagnosis, and then followed through with a neurocognitive rehabilitation plan suggested by the first author (TDE). This neurocognitive rehabilitation plan was tailored to address the specific levels of functioning that Alpha evidenced from her assessments.

We strongly recommend neurocognitive assessment and intervention for these patients, alongside newer medical interventions. The lack of continued neurocognitive decline from age 13–11 to age 15–0 may be attributable to (1) the milder form of MPS with which Alpha was diagnosed, (2) the newer treatments initiated by the team of physicians (JM), (3) the fact that Alpha probably began life with a higher-than-average neurocognitive capacity, or (4) the supportive and appropriately challenging environment of social support that Alpha enjoyed. Undoubtedly, all four of these factors are inter-related. However, neurocognitive assessment adds a low burden to an overall treatment plan, and can help with behavioral interventions designed to improve long-term neurocognitive functioning.

References

- Brown MB. 1999. The mucopolysaccharidoses. In Goldstein S, Reynolds CR (eds). *Handbook of neurodevelopmental and genetic disorders in children*. New York: Guilford.
- Grewal SS, Krivit W, Defor TE, et al. 2002. Outcome of second hematopoietic cell transplantation in Hurler syndrome. *Bone Marrow Transplant*, 29:491–6.
- Guffon N, Souillet G, Maire I, et al. 1998. Follow-up of nine patients with Hurler syndrome after bone marrow transplantation. *J Pediatrics*, 133:119–25.
- Neufeld EF, Muenzer J. 1995. The mucopolysaccharidoses. In Scriver CR, Beaudet AL, Sly WS, Valle D (eds). *The metabolic and molecular bases of inherited disease*. New York: McGraw-Hill.
- Sattler JM. 1992. *Assessment of children*. San Diego: Jerome Sattler.
- Shapiro EG, Lockman LA, Balthazar M, et al. 1995. Neuropsychological outcomes of several storage diseases with and without bone marrow transplantation. *J Inher Metab Diseases*, 18:413–29.
- Taylor HG. 2004. Research on outcomes of pediatric traumatic brain injury: current advances and future directions. *Dev Neuropsychol*, 25:199–225.