GROSS MOTOR AND GAIT ABILITIES OF CHILDREN WITH HURLER SYNDROME, PRE AND POST UMBILICAL CORD BLOOD TRANSPLANT

By
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ABSTRACT

Stacey Chapman Dusing: Gross Motor and Gait Abilities of Children with Hurler Syndrome, Pre and Post Umbilical Cord Blood Transplant
(Under the direction of Deborah E. Thorpe)

Children with Hurler syndrome have significant impairments to body structure and function that result from glycosaminoglycans accumulating in cells throughout the body. Little is known about activity limitations or more specifically gross motor and gait abilities in this population. The advent of new treatments such as umbilical cord blood transplantation (UCBT) is increasing the lifespan of children with Hurler syndrome. Information on gross motor and gait abilities with and without medical interventions such as UCBT will enable the medical community, therapists, and families to help children with Hurler syndrome maximize their motor abilities. The purpose of this dissertation was to describe the gross motor and gait abilities of children with Hurler syndrome pre and post UCBT. The first study presents a case series of 4 children who had not received medical intervention to alter their enzyme levels. The second study describes changes in gross motor abilities over time for 21 children who received UCBT. The third study describes changes in selected gait parameters of 18 children with Hurler syndrome post UCBT. The combined results of these studies indicate that children with Hurler syndrome have below average gross motor abilities and significant joint range of motion impairments by 10 months of age. Gross motor abilities are most delayed in the area of locomotion prior to and after UCBT. Following UCBT, children with Hurler syndrome gain locomotor and object manipulation abilities at the same

or a faster rate than typically developing children. However, they gain stationary balance abilities at a rate slower than their peers. In addition, children with Hurler syndrome post UBCT walk with age appropriate velocity and step length by 48 months of age, after having immature gait at 24 and 36 months of age. The findings from this dissertation suggest that children with Hurler syndrome do have the ability to gain new gross motor abilities and improve gait velocity and step length with increasing time post-UCBT. However, significant discrepancies in the children's abilities on various gross motor domains maybe related to orthopedic conditions, strength, and balance deficits. There findings warrant further investigation.

To Tim and Cole:
For your patience, support, and love
I have learned so much from you both

To Mom, Dad, Jenn, and David:
For a lifetime of opportunities to learn

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LIST OF ABBREVIATIONS

Age	age at the time of the assessment
BMT	bone marrow transplantation
cm	centimeter
CPAP	continuous positive airway pressure
g	acceleration of gravity (9.81 meters/second squared)
GAG	glycosaminoglycans
GAS	Goal Attainment Scaling
GMQ	gross motor quotient
ERT	enzyme replacement therapy
FMQ	fine motor quotient
HIPPA	Health Insurance and Portability and Accountability Act
HSCT	hematopoietic stem cell transplantation
ICC	intraclass correlation coefficient
IUDA	alpha-L-iduronidase
PEDI	Pediatric Evaluation of Disability Inventory
PDMS-2	Peabody Developmental Motor Scale, second edition
M	mean
MDI	mental developmental index
MPS	mucopolysaccharidoses
MPS I	mucopolysaccharidoses type I
MPS I-H	Hurler syndrome
MPS I-H/S	Hurler-Scheie syndrome

MPS I-S	Scheie syndrome
MRI	magnetic resonance imaging
Ncad	normalized cadence
NFRD	Neurodevelopmental Function in Rare Disorders
Nstl	normalized step length
Nvel	normalized velocity
RLO	raw score on the locomotion subtest of the Peabody Development Motor Scales, second edition
ROB	raw score on the object manipulation subtest of the Peabody Development Motor Scales, second edition
RST	raw score on the stationary subtest of the Peabody Development Motor Scales, second edition
RSV	respiratory syncytial virus
SD	standard deviation
SE	standard error
SQRT	square route
Tage	age at the time of UCBT
TMQ	total motor quotient
TPT	time post UCBT
UCBT	umbilical cord blood transplantation
URI	upper respiratory infections

CHAPTER I

INTRODUCTION

Hurler syndrome is the most severe form of mucopolysaccharidosis type I resulting from an inborn error of metabolism. [1] Children diagnosed with Hurler syndrome have a deficiency in the lysosomal enzymes responsible for breaking down the glycosaminoglycans (GAG) heparan sulfate and dermatan sulfate. The resulting accumulation of GAG throughout the body causes significant somatic, central nervous system and musculoskeletal system impairments.[1] Children diagnosed with Hurler syndrome have significant joint contractures and malalignment of the lower extremities.[2,3]

Little is known about the gross motor abilities or activity limitations of children with Hurler syndrome. It has been reported that children with Hurler syndrome reach their maximal functional abilities by 2 to 4 years of age, followed by a gradual regression in abilities; however, these investigators provided no details on the children's gross motor abilities.[1] In addition, no one has described the relationship between lower limb joint range of motion and the ability to ambulate in this population.

Umbilical cord blood transplantation (UCBT) is a relatively new treatment option for children with Hurler syndrome with the first transplant being completed in 1998.[4] Successful engraftment and survival of 17 out of 20 patients who received UCBT to treat Hurler syndrome has been reported.[4] In these children, growth normalized, some improvement was recorded in orthopedic conditions, such as reduced or stabilized kyphosis, and most gained cognitive skills at a rate slightly slower than their peers. While UCBT has been documented to arrest the progression and reverse the effects of some of the body structure and function impairments associated with Hurler syndrome, little is known about the impact of UCBT on activity limitations such as gross motor or gait limitations.[4]

Gross motor abilities, gait abilities, and joint range of motion are reportedly limited in children with Hurler syndrome.[1,3,5] These areas are inter-related yet each provides unique information that contributes to the understanding of the gross motor abilities of children with Hurler syndrome. Joint range of motion can have a significant impact on the efficiency of gait in both healthy [6,7] and disabled [8] populations. Limited ambulatory abilities are related to decreased physical activity and decreased self-esteem in children.[9, 10] The inability to independently ambulate or the presence of gross motor delays may decrease a child's ability to participate in active, unstructured, and independent outdoor play. This type of play has been related to improved social, emotional and cognitive development.[11]

Assessment of gross motor abilities frequently includes an evaluation of the ability to ambulate.[12-14] However, standardized gross motor assessments do not assess specific temporal and spatial gait parameters that may provide evidence of immature or inefficient gait. For example, the Peabody Developmental Motor Scale, second edition (PDMS-2) includes items that assess a child's ability to walk without assistance and with a heel-toe progression.[14] However, the PDMS-2 does not consider several important determinants of mature gait such as velocity, step length or cadence.[15] Evaluating temporal and spatial gait parameters provides detailed information on gait maturity and efficiency.

A detailed description of the gross motor abilities of children with Hurler syndrome pre and post medical intervention is needed in order to understand gross motor changes in children with this syndrome. Improved understanding of the gross motor abilities of the children prior to medical intervention will help families anticipate how their decision to seek medical intervention may impact their child's gross motor abilities. Documentation of the gross motor abilities of children with Hurler syndrome prior to medical intervention will

provide a baseline with which to evaluate the efficacy of medical interventions for specific gross motor abilities.

Improved understanding of specific areas of gross motor deficit will help physical therapists working with this population to determine appropriate treatments to maximize the child's gross motor abilities and achieve independent ambulation. Data on the gross motor abilities of children with Hurler syndrome post UCBT will provide baseline data for comparison between routine care and new advances in therapeutic and/or medical interventions for this population.

Purpose

The purpose of this dissertation is to describe the gross motor abilities of children with Hurler syndrome pre and post UCBT and to document abilities on specific gross motor domains (stationary balance, locomotion, or large object manipulation) in this population.

Clinical Assessments

Children diagnosed with Hurler syndrome who were candidates for or who received UCBT at Duke University Medical Center were referred to the Neurodevelopmental Function in Rare Disorders (NFRD) program at the Center for the Study of Development and Learning at the University of North Carolina at Chapel Hill for an interdisciplinary assessment. The assessment team included neurodevelopmental pediatrics, physical therapy, speech-language therapy, audiology, psychology, and nursing. Children with Hurler syndrome were generally seen for assessment pre-transplant, 3 or 6 months post transplant, and yearly thereafter.

The physical therapists on the NFRD team were responsible for the gross motor and joint range of motion assessments. Whenever possible, the physical therapist also completed an assessment of temporal and spatial gait parameters using the GAITRite® electronic walkway. Standardized procedures for gross motor assessment and joint range of motion began in July 2002. The standardized GAITRite® procedures were added to the clinical assessment in December 2002. The data included in this dissertation were collected during clinical assessments between September 2002 and May 2005. This research was approved by the Biomedical Institutional Review Board at University of North Carolina at Chapel Hill.

The gross motor and gait abilities of children with Hurler syndrome will be described in a series of three manuscripts.

Manuscript one: Gross Motor Abilities of Children with Hurler Syndrome, A Case Series

Aim: To describe the gross motor abilities and joint range of motion in 4 children with Hurler syndrome who did not receive medical intervention to alter their enzyme levels.

Manuscript two: Gross Motor Development of Children with Hurler Syndrome, Post Umbilical Cord Blood Transplant

Aim: To describe the gross motor development of children with Hurler syndrome post UCBT.

Manuscript three: Temporal and Spatial Gait Characteristics of Children with Hurler Syndrome, Post Umbilical Cord Blood Transplant

Aims:

1) To compare the spatial and temporal gait characteristics of children with Hurler syndrome post UCBT to those of typically developing children.
2) To investigate the relationship between passive ankle dorsiflexion and knee extension and select gait parameters in children with Hurler syndrome post UCBT.

CHAPTER II

MANUSCRIPT ONE

Gross Motor Abilities of Children with Hurler Syndrome: A Case Series

ABSTRACT

Hurler syndrome is the most severe form of Mucopolysaccharidosis type I. There is a paucity of literature reporting the gross motor abilities of children with untreated Hurler syndrome. The purpose of this case series is to describe the gross motor abilities of 4 children (9.5-16 months of age) diagnosed with Hurler syndrome. The children were assessed using the Peabody Developmental Motor Scales, second edition. Gross motor delays were present in all 4 children at the time of assessment, and were most evident in locomotor abilities for 3 of the children. All 4 children had range of motion limitations at multiple joints. This case series provides evidence for early gross motor delays in this population as well as evidence concerning specific gross motor abilities of children with untreated Hurler syndrome. It is recommended that children diagnosed with Hurler syndrome be referred to physical therapy services upon diagnosis and that physical therapists be part of the interdisciplinary team involved in the care of children with Hurler syndrome.

Key Words: Hurler syndrome, case series, gross motor development

Hurler syndrome is the most severe form of Mucopolysaccharidosis type I resulting from a deficiency in lysosomal enzymes responsible for breaking down the glycosaminoglycans (GAG) heparan sulfate and dermatan sulfate.[1] The resulting accumulation of GAG throughout the body causes significant somatic, central nervous system and musculoskeletal system impairments.[1] Little is known about the gross motor abilities of children with Hurler syndrome. It has been reported that children with Hurler syndrome reach their maximal functional abilities by 2 to 4 years of age, followed by a gradual regression in abilities.[1] However, there are no reports describing children's gross motor abilities or the emergence of gross motor delays.

The purpose of this case series report is to describe the gross motor abilities and range of motion impairments of 4 children with Hurler syndrome. Improved understanding of gross motor abilities in children with Hurler syndrome will provide a baseline from which to evaluate the effects of medical interventions on gross motor abilities and to inform families about how the disease may affect gross motor abilities if untreated. Information about specific areas of gross motor deficit will assist therapists in identifying intervention strategies to maximize functional abilities.

CASE REPORTS

All four children presented in this case series were confirmed to have Hurler syndrome through blood enzyme analysis and/or genetic testing and had clinical symptoms that were consistent with a severe phenotype of Hurler syndrome. Each child's clinical records were reviewed retrospectively to document the child's clinical signs and developmental history.

This study was approved by the Biomedical Institutional Review Board at University of North Carolina at Chapel Hill.

Child A was male and the product of a full term uncomplicated pregnancy. He had multiple clinical signs of Hurler syndrome in the first 9 months of life (Table 2.1). Child A's parents reported he sat independently at 9 months of age and rolled over at 9.5 months of age

Child B was female and born full term without complications. She had respiratory syncytial virus (RSV) at 1 month of age and multiple signs consistent with Hurler syndrome (Table 2.1). Following diagnosis, magnetic resonance imaging (MRI) revealed odontoid hypoplasia without cord or brainstem compression and normal brain structures at 9 months of age. A high frequency hearing loss was documented at 9 months of age. According to her parents, child B sat at 6 months of age and rolled over at 9 months of age.

Child C was female and was born at 36 weeks gestation. She required continuous positive airway pressure (CPAP) for 6 days after delivery and spent 9 days in the neonatal intensive care nursery. She had frequent upper respiratory infections (URI) complicated by RSV and pneumonia on multiple occasions. Surgical repair of severe laryngomalacia was completed at 5 months of age after several apneic episodes requiring resuscitation. Developmentally, child C sat unsupported at 6 months of age and walked at 14 months of age.

Child D was a female born at term following an uncomplicated pregnancy. She failed her newborn hearing screen and had a small atrial septal defect and left ventricular hypertrophy with normal heart function at birth. Dysmorphic features and a gibbus deformity prompted a referral to genetics and a diagnosis of Hurler (Table 2.1). Although child D received 2 doses of enzyme replacement therapy at 7 months of age, she did not continue the recommended

course of weekly treatments secondary to difficulty with intravenous access. Child D sat independently at 7-8 months of age and stood with support by 10 months.

GROSS MOTOR ASSESSMENTS

Each of the children participated in interdisciplinary assessment at the NFRD Program as one component of a comprehensive evaluation to determine candidacy for an umbilical cord blood transplant.[2] Each child's gross motor abilities were assessed by a physical therapist using the Peabody Developmental Motor Scales, second edition (PDMS-2).[3] The PDMS-2 is a norm referenced and standardized clinical assessment tool frequently used by physical and occupational therapists to evaluate motor abilities in comparison to typically developing children. The gross motor quotient (GMQ) on the PDMS-2 is a standard score with a mean of 100 and a standard deviation of 15 and represents a comparison between a child's overall gross motor abilities and the gross motor abilities of the normative sample. The normative sample for the PDMS-2 included 2,003 children birth to 71 months of age, from 46 states and one Canadian providence and whose characteristics were representative of the United States population of children less than 5 years of age in 1997. A GMQ between 90 and 110 is average, 80-89 is below average, 70-79 is poor and less than 60 is very poor.[3] The PDMS-2 contains 4 subtests that measure gross motor abilities, 3 of which are administered to each child based on the child's age. The standard score on each subtest provides a comparison with the normative sample, with a standard score of 8-12 considered average, 6-7 below average, 4-5 poor and less than 4 very poor.[3]

Child A's GMQ was 89, indicating his gross motor abilities were below average at 10 months of age. Child A's reflex and stationary subtest standard scores were in the average

range (Figure 2.1). He was able to sit independently and play with a toy, but was unable to transition into an independent sitting position. He had righting reactions and forward and lateral protective reactions. His locomotor abilities were below average (Figure 2.1). He was able to roll between prone and supine inconsistently and was unable to commando crawl or creep. Child A had low muscle tone and mild ankle, knee and shoulder range of motion limitations (Table 2.2). In comparison, his cognitive, receptive language and fine motor abilities were age appropriate.

Child B demonstrated gross motor abilities below average at 9.5 months of age, with a GMQ of 89. She had age appropriate reflexes and stationary balance (Figure 2.1). She sat with a wide base of support with her hips positioned in lateral rotation and abduction. She could grasp her feet in supine and had righting and protective reactions. However, her locomotor abilities were below average, as she was unable to transition in/out of sitting, push up on extended arms in prone, or creep (Figure 2.1). She was very fearful when attempting lower extremity weight bearing. Child B had low muscle tone, generalized weakness, and mild shoulder and ankle passive range of motion limitations (Table 2.2). Comparatively, her cognitive, language and fine motor abilities were average or better.

At 16 months of age, child C demonstrated below average gross motor abilities for her age corrected for prematurity (GMQ of 85). Child C walked with a wide base of support, maintained good sitting balance, and could stoop and recover but used external support if available. She was able to roll a ball back and forth while sitting but had difficulty throwing a small ball while standing. Child C exhibited more pronounced distal rather than proximal muscle weakness, generalized low muscle tone, and shoulder, ankle, wrist, and elbow passive

range of motion limitations (Table 2.2). Her cognitive and language abilities were below average.

Child D was assessed at 10 months of age and achieved a GMQ of 89, indicating her gross motor abilities were below average. She had average stationary balance abilities and reflexes (Figure 2.1). She was able to sit and reach outside her base of support to grasp toys and had emerging protective reactions. Child D's locomotor abilities were below average (Figure 2.1). She was able to roll prone to and from supine but was unable to transition from prone to sitting or quadruped. She was not able to crawl or creep. When held in a standing position, child D hyperextended her knees and stood on her toes. She had normal ankle range of motion and mild shoulder and knee range of motion limitations (Table 2.2). Child D's cognition, language and fine motor abilities were age appropriate.

DISCUSSION

In infancy (9.5-16 months of age) all 4 children presented with below average gross motor abilities. Three of the 4 children (A, B, and D) demonstrated similar gross motor abilities and primarily had delays in the locomotor domain of the PDMS-2. They all were able to sit well but were not able to transition between positions or mobilize within their environment. At 16 months of age, child C had difficulty with throwing and kicking balls while maintaining her balance in standing. Lack of independent mobility and balance deficits may limit a child's ability to obtain toys and play independently. Limited independence in play and lack of mobility as the child develops may hamper environmental exploration and spatial and cognitive development.[4, 5]

All 4 children in this case series had limitations in passive range of motion. Child C had developed more extensive passive range of motion limitations in her upper extremities than the younger children. Accumulation of GAG in the wrist has been related to a higher incidence of carpal tunnel syndrome as well as joint range of motion limitations in this population.[6,7] Child B was diagnosed with odontoid hypoplasia, which is more common in children with Hurler syndrome than typically developing populations.[8] The potential for odontoid hypoplasia in children with Hurler syndrome may necessitate modification of physical therapy assessments (e.g., omission of assessments such as forward rolling) and restriction of certain recreational activities.

This case series provides evidence that children with Hurler syndrome may have below average gross motor abilities and range of motion limitations as early as 10 months of age. The oldest child in this case series had the most significant gross motor delays and range of motion limitations. The cross-sectional nature of this case series prohibits the description of change in gross motor abilities in this population over time. However, documentation of the potential for gross motor delays as early as 10 months of age supports the need for early intervention as Hurler syndrome is a progressive disorder. Referral for physical therapy services may help children with Hurler syndrome maximize their gross motor abilities and may limit the impact of their motor delays on other areas of development. Additionally, physical therapists can assist families with home exercise programs to facilitate maintenance of motor abilities, strength, and range of motion and recommend appropriate adaptive equipment while they evaluate options for medical interventions.

CONCLUSION

Children with Hurler syndrome may present with below average gross motor abilities and range of motion limitations as young as 10 months of age. Further research is needed on the longitudinal changes in gross motor abilities of children with Hurler syndrome both with and without medical intervention. Physical therapy may help children with Hurler syndrome maximize their functional abilities and maintain gross motor abilities for a longer period of time.

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Table 2.1: Subject characteristics and clinical symptoms

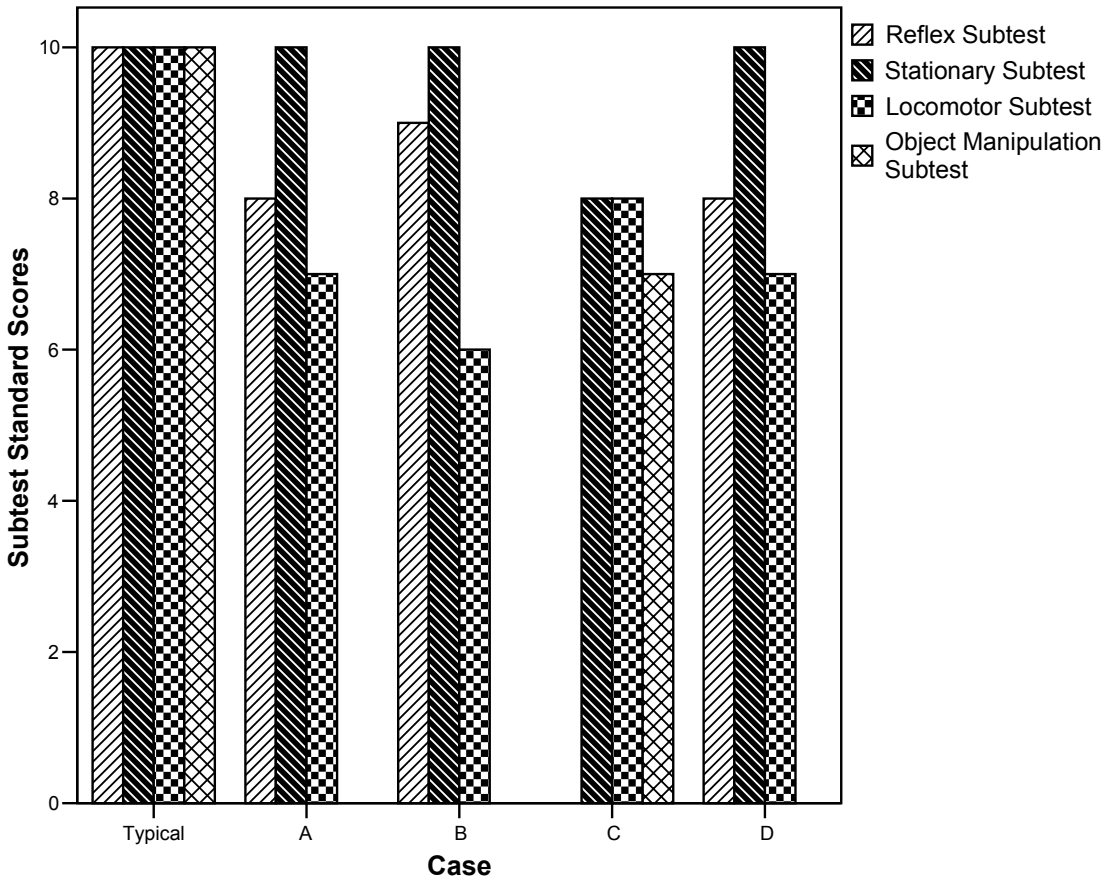
Case	Gender	Age at diagnosis (months)	Age at assessment (months)	Height (cm)	Weight (kg)	Head circumference (cm)	Clinical symptoms
A	Male	9	10	75.0	10.9	49.0	Frequent respiratory infections, hearing loss, kyphosis, corneal clouding
B	Female	6.5	9.5	72.0	20.9	47.0	hearing loss, nasal congestion, reflux, lumbar kyphosis, mitral valve prolapse, corneal clouding
C	Female	8	16	74.0	9.1	48.0	Prematurity, laryngomalacia, frequent respiratory infections, corneal clouding, heart murmur
D	Female	4	10	69.0	9.0	48.0	Hernia at birth, frequent ear and respiratory infections, hearing loss, atrial septal defect, left ventricular hypertrophy, gibbus deformity, and dysmorphic features

Table 2.2: Mean joint range of motion

Case	Age at assessment (months)	Shoulder flexion (degrees)	Shoulder-abduction (degrees)	Ankle – dorsiflexion (degrees beyond neutral)	Knee-extension (degrees)
A	10	132.5	118.5	3.5	156.5
B	9.5	131	126	15	WNL
C	16	121.5	136.5	10	171.5
D	10	139	122.5	WNL	152.5

WNL = with in normal limits on gross assessment

Figure 2.1: Peabody Developmental Motor Scale, 2nd edition subtest standard scores



CHAPTER III

MANUSCRIPT TWO

Gross Motor Development of Children with Hurler Syndrome, Post Umbilical Cord Blood Transplant

ABSTRACT

Hurler syndrome is the most severe form of Mucopolysaccharidosis type I. Little is known about the gross motor development of children with Hurler syndrome who have undergone an umbilical cord blood transplant (UCBT). The purpose of this study was to provide a detailed description of gross motor development in children with Hurler syndrome following UCBT. The longitudinal changes in gross motor abilities, as documented on the gross motor subtests of the Peabody Developmental Motor Scales, second edition (PDMS-2), are reported for 21 children for a total of 54 assessments. Children with Hurler syndrome had significant gross motor delays, with a mean gross motor quotient 2 standard deviations below the mean for a typically developing population. Children with Hurler syndrome gained abilities at the slowest rate on the stationary subtest and at the fastest rate on the locomotor subtest of the PDMS-2 after UCBT. Typically developing children would be expected to gain abilities at the same rate on all subtests. The 2 children who were transplanted prior to the onset of clinical symptoms had gross motor abilities that were more similar to their typically developing peers than those children transplanted after onset of clinical symptoms.

Key phrases: Hurler syndrome, gross motor abilities, Umbilical Cord Blood Transplantation

INTRODUCTION

Hurler syndrome is the most severe form of Mucopolysaccharidosis type I which results from an inborn error of metabolism and has an incidence of approximately 1.19 per 100,000 live births.[1,2] Children diagnosed with Hurler syndrome have a deficiency in the lysosomal enzymes responsible for breaking down the glycosaminoglycans (GAG) heparan sulfate and dermatan sulfate. The resulting accumulation of GAG throughout the body causes significant somatic, central nervous system, and musculoskeletal system impairments.[2] Children diagnosed with Hurler syndrome typically have multiple clinical signs that may include retarded growth, coarse facial features, enlarged tongues, dysostosis multiplex, joint range of motion limitations, thickening of cardiac valves, hernias, deafness, liver and spleen enlargement, corneal clouding, and abnormal hair growth. The life expectancy for children with Hurler syndrome is typically less than 10 years and mortality is usually a result of airway obstruction, respiratory infection or cardiac complications.[3] Gross motor abilities have been reported to be limited in children with Hurler syndrome who have not received medical intervention and in some who have undergone a bone marrow transplant.[2,4,5]

Umbilical cord blood transplant (UCBT) is a relatively new treatment option for children with Hurler syndrome.[6] Successful engraftment and survival was reported in 17 out of 20 patients who received an UCBT at a median age of 16 months to treat Hurler syndrome.[6] In these children, growth normalized, liver and spleen size decreased and most children gained cognitive abilities at a rate only slightly slower than their same age peers. While UCBT has been documented to arrest the progression and reverse the effects of somatic impairments associated with Hurler syndrome, there is a paucity of evidence about the impact of UCBT on the development of gross motor abilities.[4,6]

Gross motor abilities are related to a child's ability to participate in active, unstructured, and independent play which in turn has been related to improved social, emotional and cognitive development. [7] An improved understanding of the gross motor abilities of children with Hurler syndrome post-UCBT will provide the medical community and parents with information concerning the development of and potential for change in gross motor abilities following UCBT. Accurate information about motor deficits and/or recovery of gross motor abilities post transplantation may influence families' decisions to pursue an UCBT. In addition, rehabilitation professionals require more in-depth understanding of the motor abilities and deficits of children with Hurler syndrome, post-UCBT, in order to select assessment tools, develop appropriate plans of care, and utilize efficacious therapeutic interventions.

The Peabody Developmental Motor Scales, second edition (PDMS-2) is a norm-referenced and standardized clinical assessment tool that is frequently used by physical and occupational therapists to evaluate a child's motor abilities in comparison to the normative sample. [8] The normative sample for the PDMS-2 included 2,003 typically developing children birth to 71 months of age, from 46 states and one Canadian providence and whose characteristics were representative of the United States population of children less than 5 years of age in 1997. The gross motor quotient (GMQ) on the PDMS-2 is a standard score with a mean of 100 and a standard deviation of 15. A GMQ between 90 and 110 is average, 80-89 is below average, 70-79 is poor and less than 60 is very poor. [8] The GMQ of a child who is developing typically would be expected to remain stable over time, with a value of approximately 100.

The PDMS-2 has 4 subtests that measure gross motor abilities: reflexes, stationary, locomotion, and object manipulation. The standard score on each subtest provides a comparison with the normative sample and is the ideal way to compare performance on different subtests. A standard score of 8-12 is considered average, 6-7 is below average, 4-5 is poor and less than 4 is very poor. [8] For the purposes of this study *gross motor abilities* are defined as a measure of a child's abilities at any single time point, such as a child's GMQ or subtest standard score at a specific age. *Gross motor development* is a measure of how a child's abilities are changing over time and is measured using the slope of a regression line describing change in GMQ or subtest standard scores over time.

The purpose of this study was to describe the gross motor development of children with Hurler syndrome post UCBT and to document differences in specific subtests. We hypothesized that children with Hurler syndrome who were 12 and 36 months post UCBT would have GMQs less than those of typically developing children of the same age, providing evidence of gross motor delays. We selected 12 and 36 months post UCBT because most children participated in assessments close to these time points, were medically stable, and were still well within the normative age ranges for the PDMS-2. We also hypothesized that although children with Hurler syndrome might be gaining new skills or complete an increased number of individual items on the assessment, their GMQs and subtest standard scores would decrease in the first 6 months after UCBT, as the children were still recovering from UCBT and gaining abilities at a slower rate than their peers. We anticipated these children would gain abilities at a faster rate between 6 and 48 months post UCBT than during the first 6 months post UCBT. Finally, we hypothesized that the rate of gross motor development would be slowest on the stationary subtest of the PDMS-2 as children with

Hurler syndrome are likely to have orthopedic deformities such as genu valgus that may contribute to decreased stationary balance.

METHODS

Subjects

The study sample was comprised of 21 children with Hurler syndrome with a mean age at the time of assessment (Age) of 38.59±16.05 months (Table 3.1). Of these 21 children, 15 were the same children described in a previous study however gross motor development was not described.[6] Each child had 1 to 6 assessments completed during the study period between September 2002 and May 2005 yielding a total of 54 completed assessments. The object manipulation subtest included 52 observations, as one child was not assessed using this subtest at 2 of her visits secondary to not meeting age requirements for the subtest. In accordance with testing guidelines based on each child's age, only 2 assessments were included for the reflex subtest. Consequently, the reflex subtest was not included in this study

Procedures

Children diagnosed with Hurler syndrome who received an UCBT at Duke University Medical Center were referred to the Neurodevelopmental Function in Rare Disorders (NFRD) program at the Center for the Study of Development and Learning at the University of North Carolina at Chapel Hill for an interdisciplinary assessment. The assessment team included members from neurodevelopmental pediatrics, physical therapy, speech-language therapy,

audiology, psychology, and nursing. Children with Hurler syndrome were generally assessed at 3 or 6 months post transplant and yearly thereafter.

During these interdisciplinary assessments the gross motor abilities of each child less than 71 months of age were assessed by one of 3 physical therapists trained in the use of the PDMS-2. [8] Each of the 3 physical therapists assessing children with the NFRD program reviewed and scored videotaped assessments of 4 children, 3 with Mucopolysaccharidosis disorders and 1 typically developing child. Inter-rater reliability of the 3 physical therapists ranged from fair to very good (ICC [3,1] = 0.74-0.98) for the gross motor quotient, raw scores and all standard scores with the exception of the stationary subtest standard score, which had an ICC of 0.63. The lower reliability of the stationary subtest was highly influenced by the raters reporting slight differences in the number of seconds that 3 of the children could stand on one foot, a task which significantly impacts a child's standard score on this subtest. The first author (SCD) reviewed the scoring of the PDMS-2 for each assessment and used the Peabody Developmental Motor Scales Scoring and Reporting system version 1.2 to calculate all scores.

Data analysis

Mixed regression models were utilized to analyze the development of gross motor abilities. Mixed models allow for variability in the number and timing of assessments while accounting for correlations in the data from repeated measures of individual subjects.[9] Two separate regression models were fit, each to answer a separate developmental question. The first regression model described differences in gross motor abilities between children with and without Hurler syndrome at the same age and the rate of gross motor development over

time using GMQ as the dependent variable and time post UCBT (TPT) as the predictor. The second regression model was a multivariate model in which the standard scores on each of 3 gross motor subtests were the dependent variables and were used to evaluate and compare longitudinal development within and between each of the gross motor subtests. This latter model included TPT and a categorical variable designating the gross motor subtest (stationary, locomotion, and object manipulation) as well as the 2-way interaction between these variables as predictors. A final model was used to verify that the children with Hurler syndrome were gaining new abilities on each subtest. This mixed regression model used the raw score for each gross motor subtest, stationary (RST), locomotion (RLO), and object manipulation (ROB) as the dependent variables and TPT and age at transplant (Tage) as the predictors.

RESULTS

Mean age at transplant (Tage) was 17.08 ±8.45 months (Table 3.1). Of the two children without clinical symptoms prior to UCBT, one was diagnosed prenatally and the other at birth. Both children had a family history of Hurler syndrome prompting the unusually early diagnosis. Children who were transplanted prior to the onset of symptoms of Hurler syndrome were younger at the time of transplant and assessment. The majority of children presented with corneal clouding, hearing impairments, cognitive impairments, and genu valgum (Table 3.2). Seventeen (81.0 %) of the children were receiving physical therapy at the time of one or more of their assessments. Most (79.0%) of those receiving physical therapy were being treated at least weekly.

The children with Hurler syndrome had predicted GMQs below that of the normative sample on the PDMS-2, representing a typically developing population, between 0 and 48 months post-UCBT [intercept= 70.93, standard error (SE) = 2.21, $p<0.001$, Figure 3.1]. For children with Hurler syndrome there was no difference between the predicted GMQ at 12 and 36 months post-transplant. The rate of gross motor development was similar to that of the children in the PDMS-2 normative sample at the same age (slope = – 0.006, SE= 0.12, p=.96, Figure 3.1).

Over time, the children in our study with Hurler syndrome had increasing raw scores on all 3 subtests (Table 3.3). However, they had standard scores on the stationary, locomotion and object manipulation subtests that were lower than those of the children in the PDMS-2 normative sample at the same age (Figure 3.2). The changes in subtest standard scores were gradual but differed across subtests ($F_{2, 131}$=10.85, $P<0.001$, Figure 3.2). Children were the most delayed on the locomotor subtests at the time of UCBT. However, they gained abilities at the fastest rate on this subtest (slope = 0.04, SE= 0.02, p=0.09). Children with Hurler syndrome post UCBT gained skills on the object manipulation subtest at the same rate as typically developing children (slope=0.003, SE=0.02, p=0.84). However, stationary abilities improved at the slowest rate, resulting in increasing delay in this gross motor domain (slope = -0.05, SE=0.03, p=0.07).

DISCUSSION

Children with Hurler syndrome had GMQs that were on average 28.33 points lower than their typically-developing peers at the same age (mean GMQ 71.67, poor rating). As hypothesized, these children presented with significant deficits in gross motor abilities. The

rate of gross motor development could not be determined using the GMQ as planned. While the children were gaining new abilities on each subtest over time, the rate of gross motor development was different on the 3 gross motor subtests resulting in an interaction effect (Figure 3.2). The presence of this interaction effect provides evidence that the GMQ is not a detailed enough measure of gross motor abilities for children with Hurler syndrome. The individual subtests of the PDMS-2 provide a valid description of each child's abilities and should be used to describe gross motor development in this population. Use of the GMQ without considering the variation in subtest standard scores would result in an over simplification of the needs of children with Hurler syndrome post UCBT.

The slopes of the regression line for each of the 3 gross motor subtests were not statistically different from zero; however, multivariate analysis supported differences in rates of progression. Children with Hurler syndrome had the least difficulty with stationary balance tasks such as prone positioning and sitting while manipulating objects shortly after transplant. However, as stationary balance tasks became increasingly demanding, requiring standing, standing on one foot, or standing with a smaller base of support, these children had increasing difficulty, as demonstrated by a decreasing standard score on the stationary subtest of the PDMS-2. Balance and strength deficits may have contributed to difficulty with items on this subtest. For example, children frequently had difficulty standing on tiptoes without moving their feet. This may be the result of decreased lower extremity strength or balance. Genu valgum, a common problem in children with Hurler syndrome and present in 81% of the population for this study, could also have had an impact on development of stationary balance abilities. We were unable to control for the degree or timing of genu valgum onset or strength in our analysis because of the small sample size and lack of quantitative

assessment. Further research is needed to document the relationship between genu valgum, strength, balance, and gross motor abilities in this population.

Locomotor abilities such as transitioning in and out of sitting, creeping, and walking were the most delayed after transplant. Children with Hurler syndrome frequently have large heads in comparison to the rest of their bodies, many have increased intracranial pressure, and significant overall weakness. Difficulty lifting and maintaining their heads against gravity in prone and sitting may contribute to difficulties transitioning between positions. In addition, a history of hydrocephalus, increased intracranial pressure, and hearing impairments may result in balance deficits that impair locomotion. [10] Prolonged periods of time in the hospital with limited opportunities to practice mobility skills may also have contributed to these early delays. Locomotor abilities increased at the fastest rate, reducing the degree of delay in the 48 months post UCBT. Increased practice with independent mobility after hospital discharge, improved functional strength, reduced number of medications, and in some cases the initiation of therapy may have contributed to faster improvements in locomotor abilities than on other subtests. In addition, somatic and orthopedic improvements, such as smaller abdomens, improved cardiac function, or increased joint range of motion, may have contributed to improving locomotor abilities through increased endurance and reduced resistance to movement. [6]

The rate of gross motor progression on the object manipulation subtest was the same as that of a typically developing population although a significant delay persisted through 48 months post UCBT. The children in this study were generally delayed in their ability to maintain standing balance while throwing or kicking a ball. They also had difficulty throwing a ball underhand secondary to limited forearm supination.

It was hypothesized that children would gain gross motor abilities at a slower rate immediately post UCBT, followed by a gradual increase in the rate of gross motor development. However, the linear nature of the predicted models suggests that children gained abilities at the same rate in the period of time from 0 to 48 months post transplant. The mean time between UCBT and the first assessment was 16.15 months. Several children were not assessed using a standard protocol until more than 3 years post UCBT. A greater number of assessments in the 0-6 month post-UCBT range may be needed to demonstrate variability in the rate of gross motor progression immediately post UCBT. The longest a child was followed post UCBT, using the PDMS-2, was 60 months. A longer follow-up period may be required to demonstrate possible changes in the rate of gross motor progression on the gross motor subtests of the PDMS-2.

The two children who received an UCBT prior to the presentation of clinical symptoms had a mean GMQ that was greater than the mean GMQ of children who were symptomatic prior to transplant, 93.8±8.44 and 69.41±6.97 respectively. In addition, these 2 children were transplanted at a younger age (mean age 2.25±0.40 versus 18.59±7.32 months). The small number (2) of children who were transplanted in the absence of clinical symptoms reduced the generalizability of our observations for these children. Further research is needed to determine if children who are transplanted without clinical signs of Hurler syndrome will develop gross motor delays.

While we reported p-values, these analyses should be viewed within the context of population statistics. The children included in this study represent almost the entire population of children with Hurler syndrome who have undergone UCBT. Statistics using p-

values are based on sample statistics rather than descriptions of populations. Any relationships that are observed in this study are actual population relationships and only within the context of future cases can this be viewed as a sample. Clinically significant changes are more applicable than statistical differences for describing this population as descriptions will help families and health care providers understand how gross motor abilities may change after UCBT.

The cognitive abilities of the children included in this study were lower than their typically developing peers. The mean standard score for cognition was 70.68 on the Mullen Scales of Early Learning[11] or Differential Abilities Scales[12] during the interdisciplinary assessments that occurred on the same day as the gross motor assessments. The small sample size limited our ability to control for cognitive abilities in the statistical models. Keeping this in mind, we chose the PDMS-2 because the items are described using standard directions, imitation, demonstration, and in some cases facilitation through environmental manipulations, allowing for administration to children of varying cognitive abilities. In addition, children are provided with more than one trial to demonstrate performance on items, minimizing the impact of cognitive impairments on the child's performance. It has been reported [6] that a group of children with Hurler syndrome, including many of the children in this study, gained cognitive abilities following UCBT at a slightly slower rate than their peers. The results of our study and previous work [6] provide evidence that these children post UCBT may be gaining abilities across multiple developmental domains.

While the gross motor abilities of the children in this study were significantly lower than those of typically developing children, their gross motor abilities were not compared to children with Hurler syndrome who had not received an UCBT. Description of the natural

history of gross motor abilities in Hurler syndrome is limited and is no longer ethical with the availability of treatment. In addition, it is unclear what impact medical procedures such as UCBT may have on gross motor abilities in children without Hurler syndrome. It is possible that some of the motor deficits identified in this study were related to the UCBT rather than Hurler syndrome.

Physical therapists working with children or adolescents with Hurler syndrome up to 48 months post UCBT should be aware of the high probability for ongoing gross motor delays with variable rates of development in different gross motor domains. Treatment plans should include individualized goals based on the needs and functional abilities of each child. Regularly scheduled quantitative assessment, qualitative assessment, and clinical impressions should be used to gauge progress. Standardized assessments should have distinct gross and fine motor subtests, similar to the PDMS-2, as previous evidence suggests a discrepancy between fine and gross motor skills in this population.[4] Assessments focusing on activity limitation and participation, such as the Pediatric Evaluation of Disability Inventory (PEDI)[13] and Goal Attainment Scaling(GAS) [14] would also be beneficial for treatment planning and goal development. Encouraging parents, caregivers, and therapists to promote self-directed mobility and to create safe environments for independent mobility may facilitate the progression of locomotor abilities in these children. Most of the children in this study were receiving physical therapy at the time of their assessments. It is unclear as to whether physical therapy affected progression of gross motor abilities and if so, to what degree. Further research is required to describe the various types of physical therapy, orthotic, and orthopedic interventions for this population before recommendations can be made on the type, frequency, or dosage that may be the most beneficial.

CONCLUSION

Children with Hurler syndrome who are symptomatic prior to UCBT generally have significant gross motor delays through 48 months post UCBT. However, these children gain new gross motor abilities in all domains following transplant. The rate of gross motor progression varies across gross motor domains, warranting detailed assessments rather than reliance on summary scores such as the GMQ to report changes in gross motor abilities. Future research should focus on the progression of gross motor abilities beyond 48 months post UCBT, and the relationship between gross motor abilities, strength, orthopedic deformities, gait abilities, and physical therapy interventions.

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Table 3.1: Subject demographics (M ± SD)

	Number of Assessments	Height (cm)	Weight (Kg)	Number of Females	Tage	Age	TPT
Total Sample (n=21)	54	89.0± 11.2	15.11± 4.03	13	17.08± 8.45	38.59± 16.05	21.51± 14.56
Symptomatic (n=19)	49	90.0± 10.9	15.5± 4.0	11	18.59± 7.32	40.26± 15.16	21.67± 14.52
Asymptomatic (n=2)	5	79.5± 10.0	10.9± 1.7	2	2.25 ± 0.40	22.22± 16.98	19.98± 16.53

TAge = age at time of UCBT (months)
Age = age at the time of assessment (months)
TPT = time between UCBT and assessment (months)

Table 3.2: Frequency of medical conditions (n=21)

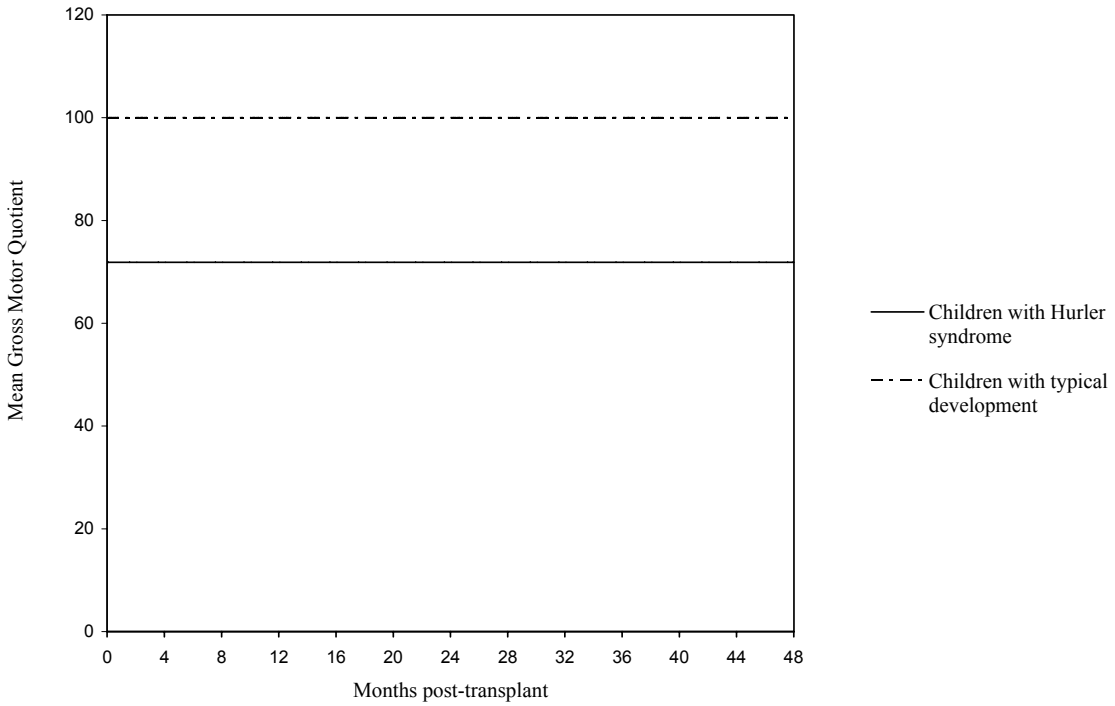
Medical Condition	Number	Percent
Hydrocephalus/shunt placement	7	33.3
Corneal Clouding	18	85.7
Hearing impairments	14	66.7
Cardiac abnormalities	9	42.9
Genu valgum	17	81.0
Cognitive impairments (standard score less than 85)	17	81.0

Table 3.3: Mixed regression model for the subtest raw scores

	RST		RLO		ROB	
	Estimate ±SE	p-value	Estimate ±SE	p-value	Estimate ±SE	p-value
Intercept	35.01±1.17	<0.001	55.83±9.22	<0.001	4.17±2.95	0.17
TPT	0.24±0.03	<0.001	2.21±0.33	<0.001	0.61±0.07	<0.001
TPT quadratic	NA	NA	-0.02±0.01	0.04	NA	NA
Tage	0.10±0.06	0.12	1.19±0.47	0.03	0.45±0.15	0.006

TAge = age at time of UCBT (months)
TPT = time between UCBT and assessment (months)
RST = raw score on the stationary subtest of the PDMS-2
RLO = raw score on the locomotion subtest of the PDMS-2
ROB = raw score on the object manipulation subtest of the PDMS-2

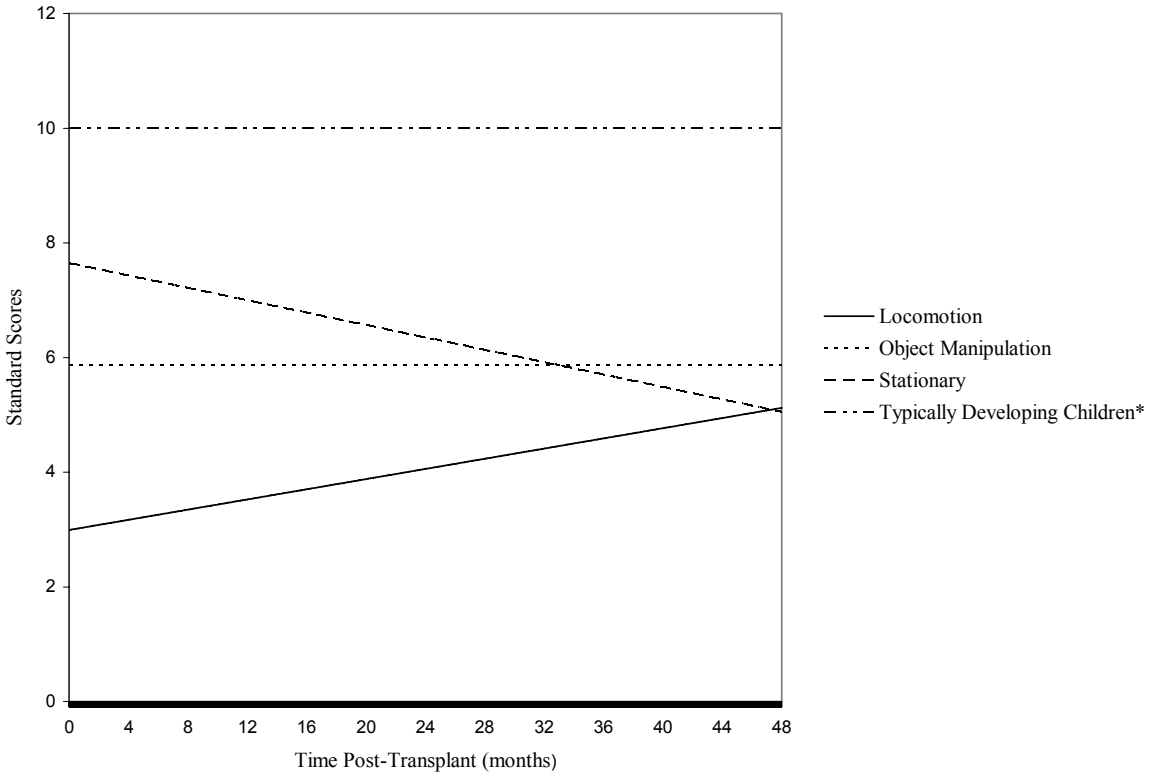
Figure 3.1: Changes in gross motor quotient post umbilical cord blood transplant



* Represents the mean gross motor quotient for a typically developing population on the Peabody developmental motor scales, second edition (PDMS-2)

Gross motor abilities are measured by the GMQ at any time point.
Gross motor development is measured by the slope of the regression line between 2 or more time points.

Figure 3.2: Subtest standard scores after umbilical cord blood transplant



* Represents the mean standard score for a typically developing population on any subtest of the Peabody developmental motor scales, second edition (PDMS-2)

CHAPTER IV

MANUSCRIPT THREE

Temporal and Spatial Gait Characteristics of Children with Hurler syndrome, Post Umbilical Cord Blood Transplant

ABSTRACT

Background and purpose: The purpose of this study was to describe the temporal and spatial gait parameters of children with Hurler syndrome following umbilical cord blood transplant (UCBT). **Subjects**: The group with Hurler syndrome consisted of 18 children between 19.6 and 96.8 months of age who were assessed over a 2.5 year period between 2.9 and 72.2 months post umbilical cord blood transplant. Four hundred and thirty eight typically developing children between the ages of 14.4 and 131.8 months served as a comparison group. **Methods:** Temporal and spatial gait parameters were assessed using the GAITRite ® electronic walkway. Knee and ankle joint range of motion was assessed for children with Hurler syndrome. **Results:** Children with Hurler syndrome had a slower normalized velocity and shorter normalized step length than typically developing children at 2 and 3 years of age. Time since transplant was a predictor of normalized velocity and step length. **Discussion and Conclusions:** Although children with Hurler syndrome post UCBT are delayed in the maturation of temporal and spatial gait parameters, they develop age-appropriate gait parameters by 4 years of age.

Key words: Hurler syndrome, gait, Mucopolysaccharidosis , umbilical cord blood transplantation

INTRODUCTION

Hurler syndrome is the most severe form of Mucopolysaccharidosis type I and has an incidence of approximately 1.19 per 100,000 live births. [1,2] Children diagnosed with Hurler syndrome typically have retarded growth, coarse facial features, enlarged tongues, dysostosis multiplex, joint range of motion limitations, thickening of cardiac valves, hernias, deafness, liver and spleen enlargement, corneal clouding and abnormal hair growth. Life expectancy for children with Hurler syndrome is typically less than 10 years. Death usually results from airway obstruction, respiratory infection or cardiac complications.[3] Gross motor abilities are frequently below average in children with Hurler syndrome and have been observed to be delayed as early as 10 months of age (S.C.D, unpublished data, 2005).

Hematopoietic stem cell transplantation (HSCT) using bone marrow or bone marrow transplantation (BMT) has been used to treat Hurler syndrome for the last 20 years. Marked improvements in somatic impairment and cognitive abilities were documented in children who were transplanted at less than 24 months of age with minimal cognitive impairment.[4] However, BMT does not appear to alter the natural history of musculoskeletal impairments in this population.[5] In addition, gross motor abilities continue to be delayed in some children who have undergone BMT.[6]

Umbilical cord blood transplantation (UCBT), a type of HSCT, is a relatively new treatment option for children with Hurler syndrome.[7] One study reported successful engraftment and survival of 17 out of 20 patients who received UCBT to treat Hurler syndrome. [7] In these children, growth normalized, kyphosis stabilized or was reduced, and most of the children gained cognitive skills, but at a rate slightly slower than their peers.[7] Additional research provided evidence that children with Hurler syndrome have significant

gross motor delays post UCBT and gain abilities at varying rates in different gross motor domains (S.C.D., unpublished data, 2005). In several pediatric populations, temporal and spatial gait parameters have been related to gait maturity and efficiency and have been correlated with gross motor abilities. [8-10] There is evidence to support a relationship between decreased lower extremity range of motion and reduced gait efficiency in both persons who are healthy [11,12] and those with disabilities.[13] Lower extremity joint range of motion and gait parameters of children with Hurler syndrome have not previously been described.

Limitations in ambulatory ability, including walking at a slow speed or needing an assistive device, are related to decreased physical activity, limited independence with community activities, and reduced self-esteem in children.[14-16] In addition, the inability to independently ambulate may decrease a child's ability to participate in active, unstructured, and independent play. This type of play appears important for social, emotional and cognitive development.[17] Many children with Hurler syndrome present with range of motion limitations and gross motor deficits, which increases their risk of developing immature or inefficient gait, ultimately leading to activity and participation limitations.

Improved medical treatments and increased survival of children with Hurler syndrome will result in a larger number of children seeking rehabilitative services than in the past. Information about temporal and spatial gait parameters of children with Hurler syndrome post- UCBT is important for members of the medical community, including therapists, in order to plan evaluation and intervention strategies. Information on gait in children with Hurler syndrome also can be used for comparison with future studies of gait following interventions such as prolonged stretching, splinting, and orthopedic procedures.

The primary purpose of this study was to compare the spatial and temporal gait characteristics of children with Hurler syndrome post UCBT to the gait characteristics of typically developing children. The secondary aim was to investigate the relationship between ankle dorsiflexion and knee extension range of motion and gait velocity, cadence, and step length in children with Hurler syndrome post UCBT. It was hypothesized that children with Hurler syndrome post UCBT would have a slower normalized gait velocity, higher normalized cadence, and shorter normalized step length than their typically developing peers at 2 and 3 years of age. A second hypothesis was that decreased ankle dorsiflexion and knee extension would be related to decreased normalized step length and normalized velocity.

METHODS

Subjects

The group with Hurler syndrome included children aged 19.6 to 96.8 months who received an UCBT to treat a diagnosis of Hurler syndrome and were referred to the Neurodevelopmental Function in Rare Disorders (NFRD) program at the Center for the Study of Development and Learning at the University of North Carolina (Table 4.1). A sample of 438 typically developing children aged 14.4 to 131.8 months was recruited from local elementary schools, preschools, daycares and the community during a previous study, and used as a comparison group (Table 4.1).[18] This study was approved by the Biomedical Institutional Review Board at University of North Carolina and met the requirements of the Health Insurance and Portability and Accountability Act (HIPPA).

Procedures

All children with Hurler syndrome who were assessed within the NFRD program between December 2002 and May 2005 and could walk 50 ft without an assistive device were included in this study. Each child's date of birth, date of transplant, date of assessment(s), height, weight, clinical characteristics, temporal and spatial gait parameters, and joint range of motion measurements were recorded at each assessment.

Temporal and spatial gait parameters for both groups of children were assessed using a standard clinical protocol and the GAITRite® electronic walkway.[a] The total distance for each walk was 7.66 meters, the middle 3.66 meters of which were on the GAITRite® walkway. The GAITRite ® walkway was connected to a laptop computer which utilized the GAITRite® Gold software version 3.4. When necessary, a parent stood at the end of the walkway to encourage the child to walk towards him/her. Each child completed 2 walks at his or her self-selected pace with at least 4 footfalls on the GAITRite® walkway. Velocity, cadence and step length were calculated using GAITRite® software.[18] Velocity, cadence and step length were normalized using non-dimensional normalization procedures described by Hof [19]and Stansfield et al[20] to reduce the effect of body stature as children with Hurler syndrome are shorter than typically developing children. The following formulae were used for non-dimensional normalization where g is the acceleration of gravity (9.81 meters/second squared) and SQRT = square root:

Normalized Step length = step length /height

Normalized velocity = velocity/SQRT(g*height)

[a] CIR Systems
MAP/CIR Inc.
1625 East Darby Road
Havertown, PA 19083
610-449-4879

Normalized cadence = cadence/SQRT(g/height)

Range of motion assessment was included in the interdisciplinary assessment within the NFRD program for all children with Hurler syndrome. In a few cases, a portion of or the entire range of motion assessment was deferred secondary to the child's inability to cooperate. Knee extension range of motion was assessed in supine with the hip flexed to 90 degrees. The axis of the goniometer was aligned with the lateral epicondyle of the femur, the fixed arm with the midline of the femur, and the mobile arm with the midline of the fibula. Ankle dorsiflexion was measured with the child positioned in supine with the hip and knee extended. The axis of the goniometer was aligned with the lateral malleolus, the fixed arm with the midline of the fibula, and the mobile arm with the lateral aspect of the 5th metatarsal. Notations were made if the child's behavior indicated pain or if the child reported pain with end range motions.

Data Analysis

A mixed regression model was utilized to compare the gait parameters of children with Hurler syndrome to the comparison group at similar ages. Mixed models allow for variability in the number and timing of assessments while accounting for correlations in the data from repeated measures of individual subjects.[21] The regression model utilized age at the time of the assessment (Age) and group membership to predict normalized velocity (Nvel), normalized cadence (Ncad), and normalized step length (Nstl). Ninety five percent confidence intervals were calculated and depicted graphically for the typically developing children to enhance the reader's ability to visualize the group differences. A separate mixed regression model was performed to determine if knee extension or ankle dorsiflexion range

of motion predicted Nvel, Ncad, or Nstl. Similar to the previous analysis, the dependent variables were the specific normalized gait parameters (Nvel, Ncad, and Nstl) and degrees of knee extension and ankle dorsiflexion. Age and time post UCBT (TPT) were the predictors.

The results of these planned analysis indicated the need for a post-hoc analysis to investigate other possible predictors of these specific gait parameters. A final mixed regression model was performed with age at the time of UCBT (Tage) and TPT as predictors of the specific normalized gait parameters (Nvel, Ncad, Nstl).

RESULTS

The comparison group included 438 typically developing children whose gait was assessed one time with no range of motion assessment. The group of children with Hurler syndrome included 18 children who were post UCBT and participated in 1 to 4 gait assessments longitudinally. Fewer range of motion assessments were completed secondary to compliance (Table 4.1). Two of the children with Hurler syndrome were diagnosed around the time of birth, received UCBT prior to presenting with clinical symptoms, and were each assessed a single time. Statistical models were not significantly different with the exclusion of the 2 asymptomatic children; therefore, their data were retained for all analyses.

Gait development of children with Hurler syndrome lagged behind that of their peers with respect to Nvel and Nstl (Figures 4.1 and 4.2, Table 4.2). Children with Hurler syndrome had slower Nvel than the comparison group at both 24 and 36 months of age (1.09 ± 0.03, $p<0.001$ and 0.47 ± 0.17, $p = 0.008$, respectively); however, the differences gradually decreased and the groups were similar by 48 months of age (0.06 ± 0.16, $p=0.70$). Children with Hurler syndrome also had a lower Nstl at 24 and 36 months of age (0.10 ± 0.02,

p>0.001 and 0.05±0.01, p>0.001, respectively), but increased their Nstl quickly to approximate their peers by 48 months (0.01±0.01, p=0.27). There were no between-group differences in Ncad, and this parameter decreased linearly for both groups at a similar rate (Figure 4.3, Table 4.2). Knee extension and ankle dorsiflexion range of motion did not predict Nvel, Ncad, or Nstl (Table 4.3). Posthoc analysis revealed that TPT, but not Tage, was positively associated with Nvel and Nstl (Table 4.4).

DISCUSSION

As hypothesized, children with Hurler syndrome post UCBT walked with a slower velocity and shorter step length than typically developing children at 24 and 36 months of age after controlling for body stature. However, their Nvel and Nstl increased rapidly to reach age appropriate values by 48 months of age. No group differences were observed in Ncad at any age as the change in Ncad with gait maturation was small in the typically developing children as well as those children with Hurler syndrome.

Children with Hurler syndrome have been documented to have delayed gross motor abilities and, in particular, difficulty with locomotor tasks both pre and immediately post UCBT (S.C.D., unpublished data, 2005). As a result, children with Hurler syndrome walk independently at an older age than typically developing children. The youngest children were 19.6 and 14.4 months of age for the group with Hurler syndrome and the comparison group, respectively. Later onset of independent walking, limited practice ambulating, and/or balance deficits resulting from vestibular dysfunction or hydrocephalus may contribute to the immature gait observed in the children with Hurler syndrome at 24 and 36 months of age.[22-24]

Follow-up analysis provided evidence that a child's age at the time of UCBT (Tage) had limited impact on the temporal and spatial gait parameters. However, time post UCBT (TPT) was a predictor of Nvel and Nstl. The mean age at UCBT was 18.8 months, an age when most children with typical development are new independent walkers. Prolonged hospitalization with limited opportunities to practice ambulation may have contributed to diminished endurance and muscle strength which may have affected the children's ability to initiate independent ambulation during this critical period for development of gait. However, following a recovery period the children with Hurler syndrome developed age-appropriate Nvel and Nstl.

Knee extension and ankle dorsiflexion range of motion did not predict temporal and spatial gait parameters of children with Hurler syndrome. However, the small number of observations that included both gait and range of motion assessment may have limited our ability to detect a relationship. Many of the children assessed in this study were fearful of the range of motion assessments. Attempts were made to conduct range of motion assessments in a non-threatening manner, including role playing with the goniometer, measuring parents prior to the assessment, and using distractions. However, more than 50% of the time the assessment had to be deferred or stopped because the child was too upset and/or the therapist did not think the measurements were reliable. Therefore, no conclusions can be made concerning the effects of knee and ankle joint range of motion on ambulation in children with Hurler syndrome.

There were several limitations to this study. The use of a typically developing comparison group, rather than a group of children with untreated Hurler syndrome limits our ability to describe the impact of UCBT on temporal and spatial gait parameters for this

population. In addition, without a comparison group of children who had similar medical procedures (UCBT) it is unclear what portion of the observed gait deficits are a result of the UCBT process rather than Hurler syndrome. While the group of children with Hurler syndrome and the comparison group were similar in gender, it is unclear if the samples were of similar racial/ethnic backgrounds. The comparison group was 74.7 percent Caucasian and all resided in one of three counties in North Carolina. Racial/ethnic data was not collected for the children with Hurler syndrome and their primary residences were scattered throughout the United States. Socioeconomic data was not available for either group. The majority of children with Hurler syndrome included in this study reported receiving physical therapy services. However, the frequency, setting (school, early interventions, or private), and type of physical therapy services were not consistent or well described by parental report limiting our ability to include therapy services in our analysis.

The children in the comparison group were assessed at a single time point and without range of motion assessments. Gait assessment was limited to 2 walks over the GAITRite® walkway. Inclusion of longer walks or practice walks might have reduced variability between walks and helped to insure that the children were walking at their actual self-selected speeds. The questionable reliability of the joint range of motion assessments in some children may have reduced our ability to detect a relationship between selected range of motion measurements and gait parameters. In addition, specific balance and strength measures were not included in the clinical protocol, limiting our ability to assess relationships between strength, balance, and gait parameters. Assessment of hearing impairments, vestibular dysfunctions, and hydrocephalus should also be included in future studies.

Although we reported p-values, these analyses should be viewed within the context of population statistics. At the time of this study, the included children represented almost the entire population of children with Hurler's syndrome who had received an UCBT and were ambulatory. Statistics using p-values are based on sample statistics, reducing their value when a population, rather than a sample that represents the population, is being described.

The results of this study provide evidence that 4- to 6-year-old children with Hurler syndrome who received UCBT between 2.1 and 43.9 months of age can ambulate with near normal velocity, cadence and step length for their height. There is also evidence that these children are able to maintain near normal temporal and spatial gait parameters through 6 years of age. Although typically developing children achieve and maintain adult like gait at 7-10 years of age, children with Hurler syndrome post-UCBT may or may not have similar gait outcomes. Orthopedic deformities such as genu valgum and/or hip dysplasia have been documented in children with Hurler syndrome post BMT and may also be present post UCBT.[5] Further research is needed to assess the presence and impact of orthopedic deformities post UCBT, and to document qualitative aspects of gait. Longitudinal post UCBT assessment of joint range of motion in these children will improve the ability to analyze this variable in the future. As children with Hurler syndrome age, they may be less fearful of range of motion assessments, thereby increasing the number of assessments that can be completed reliably.

CONCLUSION

The results of this study provide evidence that children with Hurler syndrome post UCBT have less mature gait than typically developing children at 24 and 36 months of age after

controlling for body stature. The positive relationship between time post UCBT, velocity, and step length provides evidence that the more time post transplant, the more typical the child's temporal and spatial gait parameters. Recovery from the transplant process, increased opportunities for ambulation, increased strength and/or range of motion may each have contributed to the maturation of gait documented in the study. Further research is needed on the benefits of physical therapy intervention, strength and range of motion programs and out of bed activities to facilitate gait maturation in children with Hurler syndrome post UCBT.

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Table 4.1. Subject information and select normalized gait parameters

	Entire sample	Children with Hurler syndrome	Comparison group
Subjects in sample	456	18	438
Observations in sample	477	39	438
Age[a] (M±SD)	79.10±31.23	48.62±17.67	81.82±30.74
Tage[b] (M±SD)	NA	18.75±8.52	NA
Height (cm) (M±SD)	117.77±19.13	95.15±9.72	119.79±18.46
Weight (kg) (M±SD)	25.67±11.65	17.07±3.90	26.44±11.80
Female (%)	44.7	44.4	44.7
TPT[c] (M±SD)	NA	29.87±2.91	NA
Nvel[d] (M±SD)	3.49±0.77	3.20±1.10	3.51±0.73
Ncad[e] (M±SD)	501.64±73.89	511.54±119.22	500.75±668.57
Nstl[f] (M±SD)	0.41±0.06	0.37±0.08	0.42±0.05
Knee extension[g] (M±SD) (19 observations)	NA	161.87±11.90	NA
Ankle dorsiflexion[g] (M±SD) (29 observations)	NA	12.22±8.30	NA

[a]Age = Age at the time of assessment in months
[b]Tage = Age at the time of UCBT in months
[c]TPT = Time post transplant in months
[d]Nvel = normalized velocity
[e]Ncad = normalized cadence
[f]Nstl = normalized step length
[g]Ankle and Knee range of motion recorded in degrees

Table 4.2. Mixed regression models with group and age as predictors of select normalized gait parameters.

	Nvel[b]		Ncad[c]		Nstl[d]	
	Estimate±SE	p-value	Estimate±SE	p-value	Estimate ±SE	p-value
Intercept	3.45 ± 0.16	<0.001	511.86 ± 11.59	<0.001	0.39 ± 0.01	<0.001
Group	0.06 ± 0.16	0.70	6.12 ± 12.65	0.63	0.01 ± 0.01	0.27
Age[a] linear	0.03 ± 0.008	0.0001	-0.51 ±0.11	<0.001	0.004 ± 0.0005	<0.001
Age quadratic	-0.0009 ±0.0003	0.005	NA	NA	-0.00007 ± 0.00002	0.0004
Age * Group	-0.03 ±0.009	0.004	NA	NA	-0.002 ±0.0006	<0.001
Group * age quadratic	0.0007 ± 0.0003	0.02	NA	NA	0.00006 ± 0.00002	0.004

[a]Age = Age at the time of assessment in months
[b]Nvel = normalized velocity
[c]Ncad = normalized cadence
[d]Nstl = normalized step length

Table 4.3. Mixed regression models for ankle and knee range of motion, age at assessment and time post-transplant as predictors of select normalized gait parameters

	Nvel[d]		Ncad[e]		Nstl[f]	
	Estimate±SE	p-value	Estimate ±SE	p-value	Estimate±SE	p-value
Intercept	4.77 ± 3.05	0.14	1022.52 ± 401.57	0.02	0.22 ± 0.17	0.21
Knee extension[a]	-0.010± 0.02	0.63	-3.83 ± 2.57	0.16	0.001±0.001	0.25
Ankle dorsiflexion[a]	0.009 ± 0.03	0.74	-0.58 ±3.58	0.87	0.002± 0.002	0.24
Age[b]	0.005±0.05	0.93	-5.78±6.43	0.39	0.004± 0.003	0.19
TPT[c]	0.002 ±0.05	0.96	4.61±6.96	0.52	-0.002± 0.003	0.53

[a]Ankle and Knee range of motion recorded in degrees
[b]Age = Age at the time of assessment in months
[c]TPT = Time post transplant in months
[d]Nvel = normalized velocity
[e]Ncad = normalized cadence
[f]Nstl = normalized step length

Table 4.4. Mixed regression models for age at transplant and time post-transplant as predictors of select normalized gait parameters.

	Nvel[c]		Ncad[d]		Nstl[e]	
	Estimate±SE	p-value	Estimate ±SE	p-value	Estimate±SE	p-value
Intercept	3.56 ± 0.22	<0.001	543.47 ± 24.54	<0.001	0.39 ± 0.01	<0.001
Tage[a]	-0.008± 0.04	0.83	-3.80 ± 3.95	0.34	0.002 ± 0.002	0.44
TPT[b] linear	0.04 ± 0.01	0.002	2.22 ±1.39	0.12	0.004 ± 0.0008	<0.001
TPT[b] quadratic	-0.001 ±0.0005	0.02	-0.11±0.05	0.05	-0.00008 ± 0.00003	0.01
Tage[a]* TPT[b] linear	-0.0008 ±0.002	0.66	-0.01±0.19	0.94	-0.0001± 0.0001	0.36
Tage[a] * TPT[b] quadratic	2.19E-6 ± 0.00006	0.97	0.0006±0.007	0.93	6.31E-7 ± 3.88E-6	0.87

[a]Tage = Age at the time of UCBT in months
[b]TPT = Time post transplant in months
[d]Nvel = normalized velocity
[d]Ncad = normalized cadence
[e]Nstl = normalized step length

Figure 4.1: Changes in normalized velocity (Nvel)

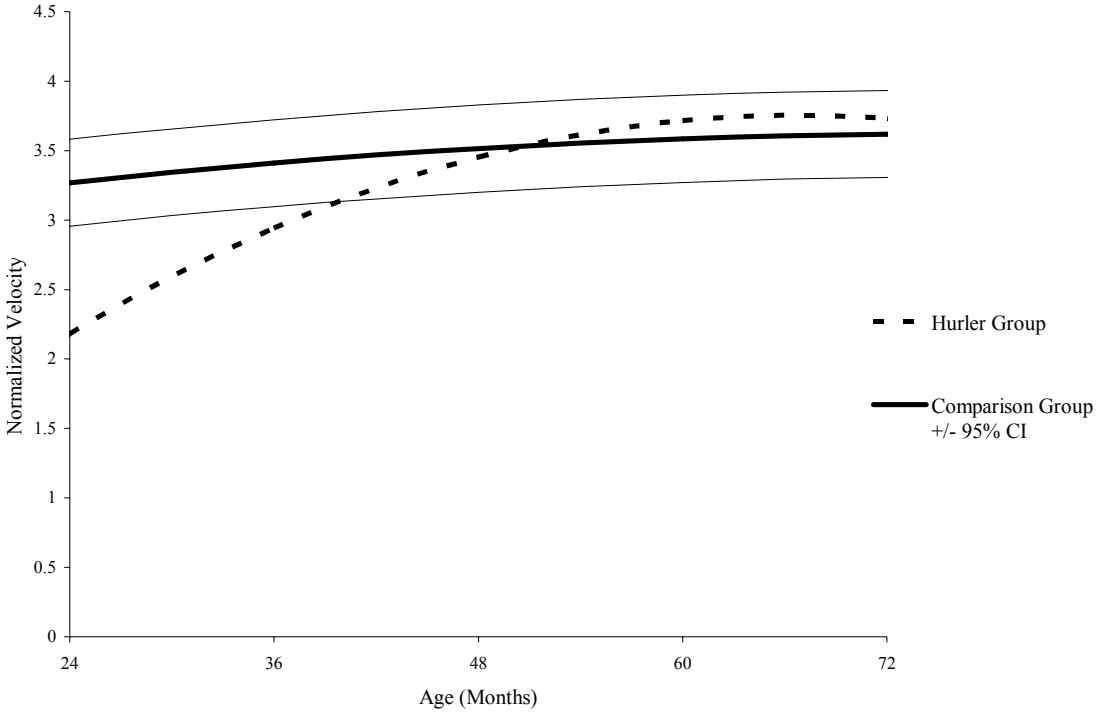


Figure 4.2: Changes in normalized step length (Nstl)

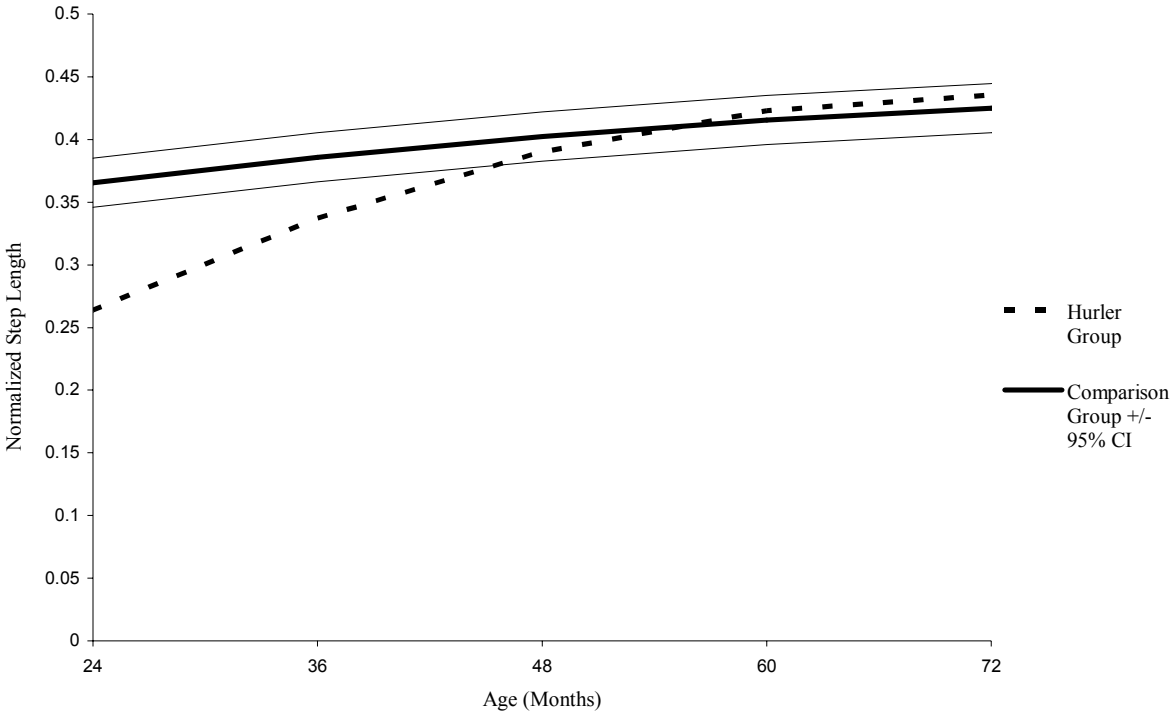
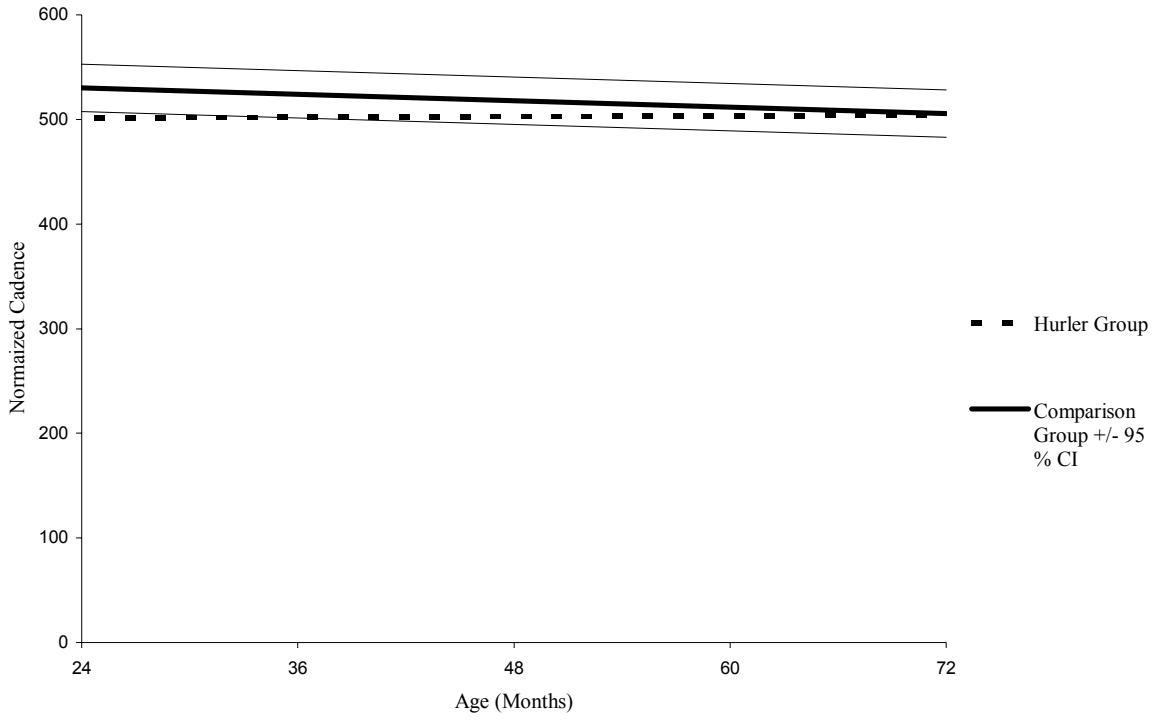


Figure 4.3: Changes in normalized cadence (Ncad)



CHAPTER V

SYNTHESIS OF DISSERTATION

The purpose of this dissertation was to describe the gross motor abilities of children with Hurler syndrome pre and post umbilical cord blood transplantation (UCBT) and to document specific gross motor abilities. The dissertation was presented in the form of 3 inter-related manuscripts, each addressing individual aims.

Summary of Findings

Manuscript 1: Gross motor abilities of children with Hurler Syndrome, a case series

Aim: To describe the gross motor abilities and joint range of motion in 4 children aged 9.5 to 16 months, with Hurler syndrome, who had not received medical intervention to alter their enzyme levels.

Findings: The gross motor abilities of these children with Hurler syndrome were below average as compared to the normative sample used in the development of the Peabody Developmental Motor Scales, second edition (PDMS-2). Ability to move in the environment (locomotor abilities) was most limited in 3 of the 4 children. In addition, all 4 children had significant joint range of motion limitations.

Manuscript 2: Gross motor development of children with Hurler syndrome post umbilical cord blood transplant

Aim: To describe the gross motor development of children with Hurler syndrome post UCBT.

Findings: Children with Hurler syndrome post UCBT had gross motor abilities that were on average 1.9 standard deviations below the mean for typically developing

children of the same age. The rate of gross motor development was not the same for all gross motor subtests of the PDMS-2. Children with Hurler syndrome post UCBT were the most delayed in their locomotor abilities following transplant. They gained abilities the quickest in the locomotor domain, reducing the degree of delay slightly by 48 months post UCBT. In contrast, stationary abilities were the least delayed in these children post UCBT, however improved at the slowest rate, therefore increasing the degree of delay by 48 months post UCBT. Children post UCBT gained abilities in the object manipulation domain at the same rate as typically developing children.

Manuscript 3: Temporal and spatial gait characteristics of children with Hurler syndrome post umbilical cord blood transplant

Aims:

1) To compare the spatial and temporal gait characteristics of children with Hurler syndrome post UCBT to those of a typically developing sample.
2) To investigate the relationship between passive ankle dorsiflexion and knee extension with select gait parameters in children with Hurler syndrome post UCBT.

Findings: Children with Hurler syndrome ambulated at a slower normalized velocity and with shorter step lengths than typically developing children at 24 and 36 months of age. However, by 48 months of age their normalized velocity and step length were similar to those of typically developing children. There were no group differences in cadence at any age. Knee extension and ankle dorsiflexion range of

motion were not predictive of velocity, cadence or step length. However, time post transplant was a predictor of velocity and step length. As the time post UCBT increased, the gait of children with Hurler syndrome became more similar to the gait of typically developing children.

Significance of Findings

The results of this research will be helpful to physicians, therapists, parents, families and individuals with Hurler syndrome. Clinical descriptions of children with Hurler syndrome typically report that these children have multiple clinical signs or body structure limitations that may include; retarded growth, coarse facial features, enlarged tongues, dysostosis multiplex, joint range of motion limitations, thickening of cardiac valves, hernias, deafness, liver and spleen enlargement, corneal clouding and abnormal hair growth.[16] However, there is a paucity literature describing gross motor abilities or activity limitations in this population either with or without medical intervention.[1] The results of this dissertation provide evidence of below average gross motor abilities and range of motion limitations in children with Hurler syndrome as young as 10 months of age.

Documentation of gross motor deficits earlier than previously described in the literature will aid physicians in early identification and diagnosis of children with Hurler syndrome, and hopefully prompt referrals to physical therapy or early intervention services. Increasing awareness of the types of gross motor delays in this population should assist interventionists in recognizing the multiple clinical signs consistent with Hurler syndrome and refer these children for further evaluation.

The gross motor abilities and gait of children with Hurler syndrome improve post UCBT. Gross motor delays persist beyond 48 months post UCBT, however, the degree of delay varies between subtests and changes over time. Gait velocity and step length gradually improve and reach values of typically developing children between 36 and 48 months of age. A better understanding of gross motor and gait development in children who have received an UCBT will help medical professionals, therapists and parents understand that a child with Hurler syndrome who underwent UCBT may continue to have gross motor delays through at least 48 months post UCBT. With this knowledge, parents can make informed decisions regarding the risks and benefits of UCBT. This research provides physical therapists with a better description of the potential for gross motor progression and identifies specific areas that may need to be closely monitored throughout development. In addition, therapists can provide services or recommendations for activity programs that may be helpful in diminishing the impact of motor delays that result from inactivity during transplant and the post-transplant period.

Slow progression of stationary balance skills following transplant may be related to progression of orthopedic deformities. Documentation of difficulties with stationary balance may assist therapists and physicians considering the need for orthotic or surgical intervention. Variability in rate of progression on the gross motor subtests of the PDMS-2 provides evidence that detailed standardized assessments are required to document changes in gross motor abilities and that the use of summary scores may over simplify the gross motor development of children with Hurler syndrome. Children who are not gaining skills in specific motor domains may require increased and/or targeted therapy services.

Gross motor abilities were less delayed in children who were transplanted prior to the onset of clinical signs compared to those who were transplanted following the onset of clinical signs. Gait became more typical with increasing time post transplant. These finding suggest that earlier diagnosis and treatment has positive effects on gross motor outcomes in children with Hurler syndrome. Early screening to detect Hurler syndrome in those with a family history or as part of routine screenings at birth may increase the rate of early diagnosis and subsequent intervention, improving motor abilities and diminishing future participation limitations. Physicians and third party payers need to be aware that delaying diagnosis and treatment could negatively impact the child's long-term gross motor abilities.

Strengths and Weaknesses (Limitations)

Strengths

1) The sample included most of the population of children with Hurler syndrome who have received UCBT to date
2) Longitudinal assessment of gross motor abilities
3) Inclusion of children who were asymptomatic prior to UCBT
4) Clinically relevant outcome measures
5) Results that can be used to provide recommendations for therapeutic assessments, education, and activities for this population of children
6) Identification of need for future research

Weaknesses (Limitations)

1) Small sample from a statistical perspective.

2) Lack of standardized pre UCBT gross motor assessments on the same children who were assessed post UCBT
3) Limited length of follow-up restricted predictive models of gross motor development to 48 months post-transplant
4) Lack of statistical models for children who received UCBT prior to the onset of clinical symptoms
5) Inability to control for orthopedic anomalies (genu valgum) or cognitive abilities in the statistical models
6) Lack of specific strength, balance, or vestibular assessments in the assessment protocol

Future Research

There has been a paucity of evidence related to the gross motor abilities of children with Hurler syndrome. The advent of new and more accessible treatment options, including enzyme replacement therapy and umbilical cord blood transplant, will result in more children with Hurler syndrome seeking medical and therapeutic services. This dissertation represents the first step in documenting the specific gross motor abilities of children with Hurler syndrome. Further research is needed to document the development of gross motor abilities in children who go untreated or have not yet received medical intervention. While the cases presented in the case series were informative, they were representative of a very small number of children and larger, more controlled studies are needed.

Additional research on the gross motor development of children with Hurler syndrome is needed to document the progression of abilities beyond 48 months post-UCBT. Further

research is required on the variability in rate of gross motor development on various gross motor domains and possible causes of declining rate of progression for stationary balance in this population. Research addressing the impact of interventions such as orthopedic surgeries and physical therapy are needed to enhance the knowledge base of clinicians working with this population and aid families in advocating for themselves and their children. Most importantly, research is needed on the ability of this population to participate in age appropriate community activities and to thrive as independent adolescents and adults.

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APPENDIX: LITERATURE REVIEW

The ability of a child to move independently within the environment is important to his/her social and cognitive development.[1] Children who have disabilities are less likely to have independent mobility than their non-disabled peers. A clear understanding of a child's specific abilities and limitations will help caregivers modify the environment and their expectations and assist the child to reach his\her full potential.[2] The gross motor abilities of children with rare metabolic disorders such as Hurler syndrome have not been well documented, limiting therapists' abilities to make recommendations regarding gross motor abilities and environmental modifications for this population.

SECTION 1: MUCOPOLYSACCHARIDOSES

Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by deficiency of enzymes catalyzing the breakdown of glycosaminoglycans (GAG or mucopolysaccharides).[3] Enzyme deficiencies can be present singly or in combination. The accumulation of GAG in the lysosomes results in cell, organ and tissue dysfunction. There are 11 known enzyme deficiencies that result in 7 distinct syndromes and subtypes. The MPS share some clinical features, but are variable in exact features and severity.[3] The prevalence of each MPS varies. The birth prevalence of all MPS in the Netherlands was estimated at 4.5 per 100,000 live births between 1970 and 1996.[4] Mucopolysaccharidosis type I (MPS I) was the most common MPS disorder, with a calculated birth prevalence of 1.19 per 100,000 live births. [4]

Mucopolysaccharidosis Type I

MPS I is an autosomal recessive syndrome characterized by a primary lysosomal hydrolase alpha-L-iduronidase (IUDA) deficiency. [3,5,6] IUDA is responsible for breaking down two specific types of GAG, heparan sulfate and dermatan sulfate. Therefore, IUDA deficiency results in an accumulation of heparin and dermatan sulfate in the parenchymal and mesenchymal tissues and storage of lipids in neuronal tissues. [3,5,7] Children diagnosed with MPS I present with a wide variety of clinical sequelae with three defined clinical entities. Clinical phenotypes cannot be determined biochemically by routine diagnostic procedures because all three phenotypes excrete the same GAG into the urine and have the same deficiency in IUDA. Mutation analysis can allow for classification of some children; however, clinical manifestation, including rate of progression, is most commonly used to assign children to a phenotype.[3]

The mildest phenotype of MPS I is Scheie syndrome (MPS I-S). Symptoms of Scheie syndrome usually become apparent after 5 years of age with diagnosis between 10 and 20 years of age and life expectancy into adulthood. [3] Children with Scheie syndrome may have joint stiffness, aortic valve disease, corneal clouding and few other somatic features. Later in life, obstructive airway disease may warrant a tracheotomy and valve replacements may improve cardiac function.

Hurler-Scheie (MPS I-H/S) is an intermediate phenotype between Hurler and Scheie syndromes. It is characterized by progressive somatic involvement, skeletal abnormalities and minimal intellectual dysfunction with onset of symptoms between 3 and 8 years of age. Corneal clouding, joint stiffness, deafness and heart disease generally develop by the early to

mid teenage years in these children. Survival into young adulthood is common with cardiac and respiratory compromise causing most premature mortality.[3]

Hurler syndrome (MPS I-H) is the most severe phenotype of MPS I. Children diagnosed with Hurler syndrome typically have retarded growth, coarse facial features, enlarged tongues, dysostosis multiplex (common skeletal abnormalities in this population to be described in the next section), joint range of motion limitations, thickening of cardiac valves, hernias, deafness, liver and spleen enlargement, corneal clouding and abnormal hair growth. Children with hydrocephalus may experience increased intracranial pressure requiring shunting. Life expectancy for children with Hurler syndrome is typically less than 10 years and death usually results from airway obstruction, respiratory infection or cardiac complications. [5]

Hurler Syndrome

Children diagnosed with Hurler syndrome typically have an array of musculoskeletal abnormalities, collectively known as dysostosis multiplex.[3] Dysostosis multiplex includes a large skull with thickened calvarium, premature suture closure, shallow orbits, abnormal teeth spacing, hypoplasia of the vertebrae with kyphosis, hypoplasia of the odontoid with atlanto-axial subluxation,[9] enlarged diaphyses of the long bones with poorly defined metaphyses and epiphyseal, short thick clavicles, small femoral heads and oar shaped ribs. The exact cause of these abnormalities in Hurler syndrome is unknown; however, some research has suggested that skeletal abnormalities arise from a lack of skeletal remodeling resulting in disorganized columnar architecture in the growth plates.[8] Heparan sulfate and dermatan sulfate are a part of normal cartilage and accumulation of GAG in the cartilage

may result in decreased resilience and ability to accommodate to compressive stresses, leading to joint dysfunction.[8]

Lumbar kyphosis is frequently present at birth and may be the result of anterior-inferior fractures and hypoplasia of the antero-superior aspects of the vertebral bodies.[10] The kyphosis typically progresses and often requires intervention such as a posterior spinal fusion. The pelvis of children with Hurler syndrome is usually poorly formed with significant hip dysplasia which may be present at birth or develop over time. Masterson et al[11] documented severe acetabular dysplasia and irregular ossification of the superomedial portion of the femoral head in children after bone marrow transplant (BMT). The cause of this abnormal progression in spite of BMT is unclear. Silveri et al[8] speculated that the articular and growth plate cartilage provide relative barriers to the transport of diffuse corrective enzymes present after BMT.

Genu valgum develops in the first 2-5 years of life independent of BMT.[12] The pathomechanics of the genu valgum are not completely understood, however, a failure of ossification of the lateral aspect of the tibial metaphysis and faster medial growth may contribute to the progressive nature of this lower extremity malalignment. Medial epiphyseal stapling for genu valgum has had modest success in preventing progression and reducing genu valgus in some children with Hurler syndrome after BMT.[12]

Carpal tunnel and trigger digits are more common in children with Hurler syndrome than in typically developing populations. Van Heest et al[13] reported thickening of transverse carpal ligaments with significant flexor tenosynovial deposits resulting in median nerve compressions during surgical treatment of several children diagnosed with Hurler syndrome and carpal tunnel syndrome. Routine nerve conduction velocity testing is recommended as

children with Hurler syndrome do not exhibit typical symptoms of carpal tunnel.[13,14] Early surgical intervention for carpal tunnel and trigger finger has been shown to improve function and limit muscle atrophy in this population.[13,15]

Children with Hurler syndrome frequently have some degree of hearing loss which is probably the result of mixed conductive and sensorineural components.[3,16] Hearing aids are helpful in some children. Improvements in both conductive and senorineural hearing losses have been reported following bone marrow transplantation.[17] Ocular changes in Hurler syndrome include corneal clouding, optic nerve atrophy, and retinal pigment degeneration.[18,19] Corneal clouding improves for some children after bone marrow transplantation, however, both corneal clouding and optic atrophy usually continue to progress.[18-20]

Persistent cognitive deficits are present in most children with Hurler syndrome who have not received medical treatment.[21] Shapiro et al[21] reported the mean Mental Developmental Index (MDI) on the Bayley scales of infant development[22] for children with untreated Hurler syndrome was 80 for a sample of 15 children under 2 years of age and 61 in a sample of 6 children over 2 years of age. Changes in cognitive abilities after bone marrow transplant are unclear. Peters et al[23] reported little decline in cognitive scores for children with an MDI greater than 70 prior to transplant and progressive cognitive decline for children transplanted at greater than 24 months of age or with an MDI less than 70. However, Phipps& Mulhern[24] reported concern with the method of calculating the cognitive function in this study.

Gross motor development in children with Hurler syndrome

Children with Hurler syndrome frequently have developmental delays by 12 to 24 months of age.[3] Maximal functional abilities in children with Hurler syndrome are obtained by 2 to 4 years of age followed by a gradual regression in skills in the later stages of the disorder.[3] There is no published evidence describing the standardized gross motor abilities of children with Hurler syndrome prior to medical intervention such as BMT, enzyme replacement therapy (ERT), or umbilical cord blood transplantation (UCBT). Hugh-Jones[25] presented a series of case studies reporting the psychomotor development of children with Hurler syndrome 2 years post BMT. The percentiles of items completed on a standardized developmental assessment, the Ruth Griffith Serial Assessment Scale,[25] were reported for 5 children over a series of longitudinal assessments. At their last post-transplant assessment, 3 of the 5 children had a lower percentile of gross motor items completed than prior to the BMT. In all 5 children, motor skills appeared to be an area of concern. [25] This paper did not provide data on the severity of each child's orthopedic or somatic disease nor on pre or post – transplant skill levels. Without comparison to a normative sample it is unclear how the subjects compared to their typically developing peers. [25]

Medical Treatment Options for Children with MPS I

Enzyme-replacement therapy (ERT)

ERT was approved by the Food and Drug Administration for the treatment of MPS I in April of 2003 and requires weekly infusions of recombinant IUDA. The recombinant IUDA breaks down the accumulated GAG throughout the body. ERT has facilitated clinical and biochemical improvements in children diagnosed with MPS I. [26,27] However, the lack of

enzyme transference to the central nervous system may limit the benefits of this treatment for children diagnosed with Hurler syndrome.[27] In addition, some children may develop an immune intolerance requiring close monitoring until their bodies develop a tolerance to the recombinant human IUDA.[28] ERT is currently being recommended for children who have Hurler-Scheie and more severe forms of Scheie syndrome.[29]

Bone Marrow Transplantation

Bone marrow transplantation (BMT) is the process by which a person's bone marrow is ablated and replaced by donor cells. The donor cells take over the role of the host's own bone marrow. In the case of MPS disorders, the new bone marrow produces cells that have the missing lysosomal enzymes.[30] The enzyme from the donor cells helps to break down the GAG that is produced by the host cells. The exact mechanism of the enzyme sharing is unclear.[31] BMT has been successful at halting progression of most aspects of Hurler syndrome.[17,23,25,32,33] However, in most cases, musculoskeletal disease progression continues after BMT.[11,12]

While the results of BMT are promising, finding a bone marrow donor can be very difficult and treatment has higher risks for children without a genotypically matched sibling marrow donor.[23] Children without a complete donor match are more likely to have severe graft-versus-host disease.[34] BMT typically requires the use of chemotherapeutic agents and total body irradiation to ablate the bone marrow. Total body irradiation has been associated with a decline in neuropsychological functioning, such as verbal reasoning skills and language skills, 5 to 10 years after BMT secondary to the toxic effect on neuronal development in children. [35]

Umbilical Cord Blood Transplantation

A promising new treatment for children with Hurler syndrome is hematopoietic stem cell transplantation (HSCT) using umbilical cord blood, referred to as umbilical cord blood transplantation (UCBT). The first UCBT was conducted in 1998 for this population.[36] The physiology of UCBT is the same as that of BMT; however, umbilical cord blood rather than donor bone marrow is responsible for repopulation of the host's bone marrow. Once the host's bone marrow has been repopulated or the cells have engrafted, the donor cells produce the missing lysosomal enzymes and assist with the degradation of the accumulated GAG. UCBT has been successfully used to treat both children and adults for whom a HLA-match bone marrow donor could not be found.[37-39] DeGasperi et al[40] found that the IUDA levels in umbilical cord blood samples were similar to those found in adults who are not carriers for Hurler syndrome. Similar enzyme levels support the potential use of umbilical cord blood as a source for HSCT in MPS I.

UCBT has been successfully used to treat Hurler syndrome without the use of total body irradiation, reducing the risk of UCBT compared to BMT.[36] Staba et al[36] reported successful engraftment and survival of 17 out of 20 patients who received a UCBT to treat Hurler syndrome. In these children, growth normalized, some children had improvement of their orthopedic conditions and most children gained cognitive skills but at a rate slightly slower than their peers.

Summary of Treatment Related Issues for Hurler Syndrome

Medical interventions for MPS I have always been limited. ERT appears to have excellent potential as a treatment for children with Hurler-Scheie and Scheie syndromes. However, the limited impact of ERT on cognitive function make it a less than ideal intervention for children with Hurler syndrome. Both BMT and UCBT carry significant risks of mortality. The reduced risks of mortality, graft versus host disease and the increased accessibility to umbilical cord blood support the use of UCBT rather than BMT to treat children with Hurler syndrome.[43] However, little information is available on developmental outcomes following UCBT. [36] No information has been published on the changes in motor abilities of children with Hurler syndrome after UCBT.

The decision for a child to undergo a BMT or UCBT is a difficult one for parents. Both parents and children may exhibit significant symptoms of stress during the transplant procedure.[41,42] Although parents are generally given adequate information about the transplant procedure, the lack of other treatment options limits their ability to decline intervention.[44,45] Prows and McCain[45] reported that parents sought out information on the natural history of diseases or wanted to speak with parents of children who had not received a transplant before making a decision about BMT for their child. Detailed information on progression of motor skills without treatment and following UCBT will aid medical teams and parents weighing the risks and benefits of UCBT.[30] In addition to increasing our understanding of the benefits of UCBT, improved understanding of the gross motor deficits that persist or develop following UCBT could lead to improved orthopedic management and more targeted physical therapy interventions.

SECTION 2: EVALUATING MOTOR OUTCOMES

Standardized motor assessment tools must be used to assess the motor abilities of children with Hurler syndrome. Standardized testing entails the assessment of each individual using the same items, directions and conditions.[46] Physical and occupational therapists are gradually incorporating standardized testing into their clinical practices.[46] Observational assessments are less reliable;[46] therefore, standardized testing remains the ”gold standard” for diagnosing motor disabilities and measuring progress. Four components of gross motor ability are: speed, static and dynamic body balance, coordination and strength. These components form the foundation for many standardized assessments using by physical and occupational therapist focusing on gross motor abilities. [47]

There are three primary purposes for using a standardized assessment; 1) to determine if a child is functioning differently from his/her peers (discriminative), 2) to classify children based on his/her future status (predictive) or, 3) to evaluate change over time or as the result of an intervention (evaluative).[48] In choosing a standardized assessment for use in the clinical or research setting, the following psychometrics and testing characteristics are taken into consideration: 1)purpose of the test, 2) test reliability, 3) test validity, 4) the target population, and 5) the testing environment.

Measurement Issues in Hurler Syndrome

Children diagnosed with Hurler syndrome present with limitations in gross motor abilities, difficulty walking, and joint range of motion restrictions. Previous research[3] has not provided standardized measurement of gross motor ability, gait, or joint range of motion limitations in children with Hurler syndrome pre or post UCBT.

Gross motor abilities

It is unclear as to whether the gross motor abilities of children with Hurler syndrome differ from their peers and if their motor abilities change over time. It is important that assessments used with this population have both evaluative and discriminative abilities to determine if children with Hurler syndrome have motor delays when compared to their peers and to determine if they are making progress over time. In addition, children with Hurler syndrome may have some difficulty following verbal directions secondary to hearing loss or limitations in cognition that might inhibit their ability to follow multiple step commands. A tool that allows for both verbal instructions and visual demonstration is most appropriate when active skills are being assessed in children with Hurler syndrome.

A well rested child will perform more to his/her "true" motor abilities than a child who is fatigued. However, in a clinical setting it is difficult to ensure a child is well rested prior to a gross motor assessment. Children with Hurler syndrome who are being seen for gross motor assessments as part of an interdisciplinary team assessment may be fatigued from multiple testing sessions on the same or previous days. In addition, the children may be less willing to perform tasks in an unfamiliar setting than they would be if they were being assessed at home or in a familiar therapy clinic.

Peabody Developmental Motor Scales, Second Edition

The Peabody Developmental Motor Scales, Second Edition (PDMS-2) is a standardized and norm referenced assessment tool designed for use with children from birth through 6 years of age.[49] The PDMS-2 was normed on a sample which included 2,003 children in the United States and one Canadian province during the winter of 1997 and spring 1998. The

sample was representative of the demographics reported in the 1997 U.S. Bureau of the Census Report for Children under 5 years of age. The PDMS-2 manual indicates the assessment has 5 purposes; 1) estimating motor competence compared to peers (discriminative), 2) determining disparities between gross and fine motor abilities, 3) providing qualitative and quantitative information for educational and therapy interventions for use in developing goals, 4) to evaluate progress (evaluative), and 5) in research regarding motor development and change in motor abilities.[49] The PDMS-2 is composed of 6 subtests that measure interrelated motor skills. Four subtests focus on gross motor abilities (reflexes, stationary, locomotion, and object manipulation) and are used to calculate a gross motor quotient. The other two subtests focus on fine motor abilities and visual perception (grasping and visual motor integration).

Scoring of the PDMS-2 yields a raw score, standard score, percentile ranking, and age equivalent for each subtest administered. The raw score corresponds to the number of points earned for each subtest. Age equivalence indicates which age group's mean score from the normative sample is closest to the child's raw score. The authors of the PDMS-2 manual[49] and others[50] recommend using caution when reporting age equivalence due to the frequent over interpretation of these scores and the lack of statistical rigor. Percentile rank indicates the child's relative ranking in comparison to the normative sample. The standard score represents the child's raw score compared to the mean raw score for his/her age. The standard scores for the PDMS-2 have a mean of 10 and standard deviation of 3. Standard scores are ideal for statistical analysis as the units along the scale are equally distributed.[50] The authors of the PDMS-2 recommend using the standard scores to compare performance between subtests.[49]

The gross motor quotient (GMQ), fine motor quotient (FMQ) and total motor quotient (TMQ) on the PDMS-2 have a mean of 100 and a standard deviation of 15. The quotient scores are the most reliable scores on the PDMS-2 and are the most appropriate scores to compare between children. According to the PDMS-2 manual "the GMQ measures a child's gross motor development- that is, the ability to use the large muscle system to react to environmental change, assume a stable posture when not moving, move from place to place, and catch, throw and kick balls. The FMQ measures a child's fine motor development- that is, the ability to use his or her fingers, hands and to some extent arms to grasp objects, stack blocks, draw figures, and manipulate objects." [49]

The test-retest reliability of the standard scores and the quotient scores on the PDMS-2 were assessed in two different age groups and the correlation coefficients ranged from 0.73 to .96 for 2 to 17 month olds. [49] Concurrent validity of the PDMS-2 was measured in a study with concurrent assessment of 30 children aged 1 to 11 months using the Peabody Developmental Motor Scales (the first edition) and the PDMS-2 with correlations between .84 and .91 for the gross and fine motor quotients, respectively.[49] The correlations of the Mullen Scales of Early Learning: AGS Edition and the PDMS-2 were calculated for a group of 29 children ages 2 – 6 months. The correlations between gross and fine motor composites on these two standardized tools were .86 and .80 respectively and ranged from .61 to .91 for the various subtests of the tools.[49]

The PDMS-2 is both a discriminative and evaluative standardized assessment tool. Therefore, the results of the PDMS-2 can be used to determine if children with Hurler syndrome have different motor abilities then their typically developing peers and to evaluate their motor development through a series of assessments. The PDMS-2 requires both verbal

and visual demonstration of most items and allows the rater to score some items that are facilitated by the environment, such as sitting up to obtain a toy held over head. As a result, most children with Hurler syndrome can be assessed without significant deviation from the standardized directions. The ability to score various subtests of the PDMS-2 in isolation enhances the researcher's ability to reliably compare various domains of motor abilities. Finally the PDMS-2 can be used with children from birth through 71 months of age, limiting the need to frequently transition between assessment tools.

Temporal and Spatial Gait Parameters

Gait is the primary mode of locomotion for most adults and children without disabilities. Children with Hurler syndrome may lose the ability to ambulate with or without medical and/or orthopedic treatment.[3,12] Encouraging children with Hurler syndrome to maintain their ability to ambulate is very important to quality and possibly quantity of life.[51,52] It is presently unclear if children with Hurler syndrome have age appropriate gait velocity, cadence or step length. It is also unclear how joint range of motion in this population may correlate with these gait parameters.

The ability to ambulate may have long-term effects on children's physical and mental health.[51,52] The ability to ambulate efficiently is correlated with physical activity in children with and without cerebral palsy. [53] Children with a less mature and less efficient gait, including those with cerebral palsy have lower routine physical activity levels.[53] In addition, lower physical activity levels were associated with a higher oxygen cost while walking in children with cerebral palsy, providing support for the relationship between inefficient gait abilities and reduced physical activity levels.[54] Physical activity and exercise have been

reported to improve children's self esteem and social competence.[52,55,56] Thus, children with decreased ambulatory abilities may be at risk for having reduced self-esteem and decreased social skills. Efficient gait is also positively correlated with independence with activities of daily living.[57]

The GAITRite ® System

The GAITRite[2]® system is an electronic walkway that automates the collection of spatial and temporal parameters of gait.[58] The standard GAITRite® electronic walkway contains six sensor pads encapsulated in a roll-up carpet, to produce an active area 24 inches (61cm) wide and 144 inches (366cm) long. In this arrangement the active area is a grid with dimensions of 48 sensors by 288 sensors, placed on .5 inch (1.27 cm) centers. The 12 or 16 foot walkway is portable, can be laid over any flat surface, requires minimum setup and collection time, and does not require the placement of any devices on the child. As the child ambulates across the walkway, the system captures the relative arrangement, the geometry and the applied pressure of each footfall as a function of time. The application software controls the functionality of the walkway, processes the raw data into footfall patterns, and computes the temporal and spatial parameters. The software stores each walk by patient and supports a variety of reports and analyses. The system can be utilized to test children or adults with or without shoes and assistive devices.

The validity of the GAITRite® system has been supported by studies comparing clinical gait assessment techniques including footprint studies,[59, 60,61] using shoe switches[62] and more

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technologically advanced techniques such as kinematic assessments. Bilney et al[62] also reported the inter-trial reliability for the GAITRite® at 3 speeds. ICCs ranged from 0.84-0.97 for preferred and fast speeds. ICCs were slightly lower at slower speeds ranging from 0.76-0.91. Menz et al[63] reported ICC values of 0.82 to 0.92 for walking speed, cadence, and step length in young and older adults.

Less work has been completed looking at the reliability and validity using the GAITRite with children.[61,64] Concurrent validity of the GAITRite for walking velocity, base of support, stride length, and step length with footprint studies in 4-10 year old children was reported to range from 0.86-0.99.[61] Baker et al[61] also reported a high (0.94-1.00) inter-rater reliability for multiple testers processing the same data. Good to high test-retest reliability was reported for children 1- 10 years of age for velocity and cadence. Step length was reliable in 1-7.9 year olds.[64]

Documented reliability and validity, portability, and ease of clinical use support the use of the GAITRite® system in assessing temporal and spatial parameters of gait with clinical populations. Children with Hurler syndrome who have received UCBT or BMT are immuno- suppressed for at least 12 months after transplant and are limited in their exposure to non-sterile environments. The portability of the GAITRite allows for assessment of temporal and spatial parameters in most settings and gait assessment can be completed during routine clinical visits, limiting the child's exposure to infection. Normative spatial and temporal gait parameters for typical children and adolescents using the GAITRite® system have been established.[65] This database will allow for a direct comparison between the temporal and spatial gait parameters of children with Hurler syndrome and their typically developing peers.

Joint Range of Motion

Children diagnosed with Hurler syndrome have significant joint range of motion limitations.[3] Joint range of motion limitations increase as the GAG builds up in the joint space and disrupts joint integrity.[8] In children with Hurler syndrome, it is unclear what impact joint range of motion has on gait. However, similar joint range of motion limitations have been reported to impede functional gait in other populations.[66,67,68] Hip, knee and ankle dorsiflexion contractures have been simulated in healthy adults[66] and using computer models.[67] In these simulations with adults, knee flexion contractures, similar to those of children with Hurler syndrome resulted in decreased stride length, step length and velocity. Similar associations have been documented in children with cerebral palsy.[68] Research is needed to understand the impact of joint range of motion limitations on gait in children with Hurler syndrome. If limitations in gait parameters exist for children with Hurler syndrome, there may be a heightened awareness of the need for therapeutic and orthopedic treatments to ameliorate or minimize joint range of motion limitations.

Goniometry

Goniometers are commonly used to assess joint range of motion in adults and children with both orthopedic and neurologic impairments. The reliability of goniometric measurement of joint range of motion has been investigated extensively in both children and adults.[69,70-74] Reliability of knee, [70,72,75]ankle, [69] and shoulder[71] joint range of motion measurements was variable; however, all studies reported higher intra rater reliability than inter rater reliability and suggested use of a single rater for clinical and research measurements in adults and children. Good reliability (ICC greater then .84) was

documented for inter rater reliability of ankle dorsiflexion,[72] knee flexion and extension[70,75] and shoulder flexion, abduction and lateral rotation[71] in adults. The more standardized the assessment procedures, the better the reliability of the measurements.

Measuring joint range of motion in children presents additional challenges. Children may be fearful of the procedure or may not understand the need to relax during the procedure resulting in active resistance to joint motions. In addition, children have shorter attention spans and fatigue quickly. Visual approximation of joint range of motion may be instituted to speed up assessment and limit apprehension; however, visual approximation is not a reliable measure of joint range of motion in adults or children. [69,76] Watkins et al[74] reported a standard error of measurement ranging from 4.4 to 6.5 degrees when different raters assessed ankle dorsiflexion in children with cerebral palsy and juvenile rheumatoid arthritis, respectively. The measurement error was significantly less when consistent raters were used for each assessment.[74] Kilgour et al reported mean absolute differences in joint range of motion of 7.1 degrees and 8.6 degrees for children with spastic cerebral palsy and controls respectively. Both studies included very controlled assessment procedures which may have limited their generalizability to a clinical population and setting. Kilgour et al[73] reported no increase in reliability with multiple measures and found no impact of spasticity on the accuracy of joint range of motion assessments.

The limited reliability of goniometry must be considered when this method is used to assess joint range of motion limitations in children. Whenever possible the same rater should be used for goniometric test, retest situations. The potential for measurement errors should be considered when interpreting the results of any joint range of motion measurements, especially in a clinical setting.[73] In children with arthritis, evaluators used several ordinal

measures of joint range of motion.[77-79] However, these measures are specific to the joint limitations characteristic of children with arthritis. The specificity of the measures limits their validity for use with children with Hurler syndrome and other disorders.

Summary of motor outcomes and measurement tools

Children diagnosed with Hurler syndrome present with a complex array of impairments of body structure and functions as well as activity limitations. Reliable and valid assessment of gross motor abilities, gait abilities, and joint range of motion is important for advancement of research on motor abilities in Hurler syndrome.

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