Timing is everything: Clinical courses of Hunter syndrome associated with age at initiation of therapy in a sibling pair

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Case Report

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Abstract

Hunter syndrome, or mucopolysaccharidosis (MPS) II, is a rare lysosomal disorder characterized by progressive, multi-system disease. As most symptoms cannot be reversed once established, early detection and treatment prior to the onset of clinical symptoms are critical. However, it is difficult to identify affected individuals early in disease, and therefore the long-term outcomes of initiating treatment during this optimal time period are incompletely described. We report long-term clinical outcomes of treatment when initiated prior to obvious clinical signs by comparing the courses of two siblings with neuronopathic Hunter syndrome (c.1504T>G[p.W502G]), one who was diagnosed due to clinical disease (Sibling-O, age 3.7 years) and the other who was diagnosed before disease was evident (Sibling-Y, age 12 months), due to his older sibling's findings. The brothers began enzyme replacement therapy within a month of diagnosis. Around the age of 5 years, Sibling-O had a cognitive measurement score in the impaired range of <55 (average range 85-115), whereas Sibling-Y at this age received a score of 91. Sibling-O has never achieved toilet training and needs direct assistance with toileting, dressing, and washing, while Sibling-Y is fully toilet-trained and requires less assistance with daily activities. Both siblings have demonstrated sensory-seeking behaviors, hyperactivity, impulsivity, and sleep difficulties; however, Sibling-O demonstrates physical behaviors that his brother does not, namely biting, pushing, and frequent elopement. Since the time of diagnosis, Sibling-O has experienced significant joint contractures and a steady deterioration in mobility leading to the need for an adaptive stroller at age 11, while Sibling-Y at age 10.5 could hike more than 6 miles without assistance. After nearly a decade of therapy, there were more severe and life-limiting disease manifestations for Sibling-O; data from caregiver interview indicated substantial differences in Quality of Life for the child and the family, dependent on timing of ERT. The findings from this sibling pair provide evidence of superior somatic and neurocognitive outcomes associated with presymptomatic treatment of Hunter syndrome, aligned with current considerations for newborn screening.

1. Introduction

Hunter syndrome, or mucopolysaccharidosis type II (MPS II, OMIM #309900), is a progressive disorder that affects all body systems, leading to increasing multi-organ dysfunction and shortened lifespan, as well as a worsening quality of life for the affected person and family [1–4]. This X-linked lysosomal disorder is associated with deficient activity of the enzyme iduronate-2-sulphatase (IDS, EC 3.1.6.13), which is required for complete break-down of the glycosaminoglycans (GAGs) heparan and dermatan sulfates. Continuously accumulating GAGs trigger pathogenic cascades that lead to progressive and generally irreversible clinical disease. There is considerable variability in the Hunter syndrome phenotype, in terms of both somatic and neurologic manifestations. The spectrum of functional neurologic impacts ranges from the more common neuronopathic form, which involves neurodegeneration manifesting as developmental regression and intense neurobehavioral challenges, to the non-neuronopathic form, which involves generally average intelligence and comportment [4–8]. In recent years, the non-neuronopathic form has been found to have impairments in attention and visual-motor skills [9], indicating this
Classification is not completely free of neurologic deficits as the name suggests. Severity of neurologic involvement does not predict severity of somatic disease which is always present regardless of phenotype and can be severe even in neurocognitively unaffected individuals [9–11]. The most common somatic signs include airway disease, dysostosis multiplex, joint stiffness and severely restricted range of motion, carpal tunnel syndrome, hearing loss, cardiac involvement, hepatosplenomegaly, and facial coarsening [12].

Clinical disease in Hunter syndrome steadily progresses, and as with other MPS disorders, many symptoms may be irreversible once evident [13]. Thus, it is critical to initiate treatment prior to clinical signs. In the US, the only approved treatment is intravenous infusion of recombinant IDS (idursulfase) which works to replace the deficient enzyme (i.e., enzyme replacement therapy, ERT). However, Hunter syndrome is extremely challenging to identify early in disease, as affected infants and toddlers appear physically normal, and those with the neuronopathic phenotype gain early skills before disease processes overcome development, causing regression [1, 2, 11, 14, 15]. Early detection is a critical problem. The technology is in place to identify Hunter syndrome with newborn screening (NBS) and active screening programs exist in Taiwan, Illinois and Missouri [16–18]. The advent of NBS technology, combined with the 2006 FDA approval of ERT to treat Hunter syndrome, position this disorder to be considered by the U.S. Secretary of Health and Human Services for addition to the Recommended Uniform Screening Panel (RUSP). One criterion for addition to the RUSP panel is urgency of therapy in the newborn period, but there is presently a paucity of published data documenting the long-term controlled outcomes of early versus later initiation of treatment [19]; this is partly because it has been difficult to recognize and therefore treat children with Hunter syndrome prior to clinical signs. Early disease detection prompted by diagnosis in an elder sibling proband is an important approach to understanding this critical question, as sibship genotypes are the same, phenotypes are largely similar [20, 21], and there are reduced, although not eliminated, differences in environment influencing outcomes. The present study provides a critical opportunity to describe long-term clinical outcomes of treatment when initiated prior to obvious clinical signs by comparing the courses of two siblings with neuronopathic Hunter syndrome, one who was diagnosed due to clinical disease and the other who was diagnosed before disease was evident, due to his older sibling’s findings.

2. Patients And Methods

2.1. Patients

The two brothers have the neuronopathic phenotype of Hunter syndrome, carrying c.1504T>G (p.W502G) hemizygous mutation in \( IDS \) along with undetectable iduronate-2-sulfatase enzyme activity. The parents are non-consanguineous Chinese individuals with a negative familial history for inherited diseases. The older brother (Sibling-O) was diagnosed at 3 years, 8 months old, prompting evaluation in the younger brother (Sibling-Y), who was thus diagnosed at 12 months old.

2.1.1 Treatment histories
Both brothers began receiving weekly intravenous ERT the month following diagnosis, i.e., at ages 3 years, 9 months and 13 months, respectively. They were later enrolled in a clinical trial of intrathecal (IT) idursulfase (NCT02055118) and withdrew: Sibling-O participated in the clinical trial from 6 years, 6 months old to 10 years, 2 months old while Sibling-Y participated from 5 years, 6 months old to 9 years, 9 months old. Sibling-Y began another clinical trial of CNS-penetrant ERT (NCT04251026) at 10 years, 2 months old. Sibling-O stopped all ERT at age 11 years, 8 months due to progression of neurodegeneration, and has received palliative care.

2.1.2 Birth histories and diagnosis

Sibling-O was born at 40 weeks of gestation with a birth weight of 3220 g following an uneventful pregnancy. Developmental milestones within the first year of life were met in normal timeframes, and he started to walk independently at one year. Progressive joint stiffness, clumsiness in fine motor skills, and delayed language development prompted increasing concern. By 3 years, 8 months, mucopolysaccharidosis was suspected in light of developmental delay, macrocephaly, mildly coarse facial appearance, mild hepatosplenomegaly, joint contractures and skeletal deformities. Elevated urinary GAG, undetectable IDS enzyme activity, and identification of a causative IDS allele confirmed the diagnosis of Hunter syndrome.

Sibling-Y was born at 40 weeks of gestation with a birth weight of 3180g following an uneventful pregnancy. Upon diagnosis, Sibling-Y had no apparent clinical symptoms of Hunter syndrome except macrocephaly. Developmental milestones were in the normal range at diagnosis.

2.2. Methods

A multi-method approach was used to assemble outcome data spanning approximately a decade: 1) Retrospective review of medical chart data provided by the parents from multi-disciplinary clinical records since birth; 2) Retrospective review of symptom logs recorded by the parents; 3) Virtual semi-structured interviews with the siblings’ father with focus on the boys’ lived experiences with Hunter syndrome including neurobehavioral manifestations, caregiver experiences, and overall quality of life. Within Method 1), cardiac echo reports were reviewed from the time of diagnosis and most recently; echo images were not available for review for this manuscript. This study (protocol STUDY00014051) was reviewed by the University of Minnesota Institutional Review Board, which determined it was not research requiring oversight of more than 3 human subjects as defined by DHHS and FDA regulations.

3. Results

3.1 Central Nervous System

3.1.1. Structural

On brain and cervical MRI, the structural differences between the siblings were minimal, with stability of findings over time. Both siblings had macrocephaly, mild ventriculomegaly, and enlarged perivascular
spaces in the corpus callosum. Neither sibling had shown clinical evidence of any of the following: hydrocephalus, increased intracranial pressure, seizures, cervical cord compression, myelomalacia, nor carpal tunnel syndrome. At age six, Sibling-O showed mild changes of dysostosis within the cervical spine. At age five, Sibling-Y was found to have mild cervical spinal stenosis. Findings have remained stable as demonstrated by the siblings’ most recent MRI exams performed around the age of 10 years.

3.1.2. Neurocognitive

Key neurocognitive and neurobehavioral outcomes are presented according to timing and type of treatment, i.e., before standard intravenous ERT, before enrollment in IT idursulfase, and before Sibling-Y began the clinical trial of CNS-penetrant ERT (Figure 1).

Substantial differences in neurocognitive functioning were quantified when the boys each were five years old, when they underwent neurocognitive testing to determine eligibility for the clinical trial of IT idursulfase. For this trial, an inclusion criterion was a neurocognitive score measuring between 55-85 (population mean = 100, SD = 15; average range is 85-115) on the Differential Ability Scales, Second Edition (DAS-II) [22]. Both siblings were excluded from the trial for functioning that measured outside of the eligibility range: below the range for Sibling-O, but above the range for Sibling-Y. Scores from trial screening were provided by the trial sponsor (Takeda Pharmaceutical Company Ltd) and are included with permission. Specifically, at 5.5 years old, Sibling-O received a total DAS-II score of 46. By contrast, at five years old Sibling-Y received a score of 91. Retest of Sibling-Y about three months later yielded a score of 87, again excluding him from the trial. After another three months, retest of Sibling-Y resulted in a score of 79, thus rendering him eligible to enroll in the trial. Sibling-O was regularly retested and consistently scored below 55 for the next year. However, when he reached 6.5 years old, he earned a score of 59 on the DAS-II. Parent interview indicated that his behavioral symptoms were less challenging that day and that he seemed to be feeling “collaborative” with the examiner's requests on the test items, which the parent speculated to be the factor that enabled him to earn more points. Due to this higher score, Sibling-O was eligible to be enrolled in the trial and proceeded accordingly. Post-enrollment neurocognitive testing results are not available as this is an ongoing trial.

Qualitatively, parent interview data indicate that Sibling-Y continues to remain engaged with activities requiring greater cognitive skills, such as understanding stories and movies and playing with 200-300-piece puzzles, whereas Sibling-O does not.

With respect to expressive language, at age five, Sibling-O communicated primarily via 2-3 word phrases and his vocabulary at the time was estimated at approximately 50 words. He remained verbal until the age of six, after which he has been minimally verbal, occasionally saying single words. Sibling-Y has always been more verbal than Sibling-O, according to his parents. Sibling-Y showed concerns with language skills at age seven, at which time a speech/language pathologist estimated his communication age equivalent to be that of a five- or six-year-old. An assessment at age eight indicated that Sibling-Y still used short 2-5 word phrases. His parents reported that Sibling-Y now (age 10.7) communicates at the level of a three-year-old, and that he can understand more than he can speak.
3.1.3. Neurobehavioral

Between ages four to nine, Sibling-O engaged in physical behaviors including forcefully pushing others and biting. His parents described these behaviors primarily as efforts to obtain sensory feedback and denied that the behaviors were acts of aggression, citing his overall positive outlook and happy demeanor, even when showing the behaviors. These behaviors occurred less frequently with the use of medications (including various trials of antipsychotics, hypotensive agents and psychostimulants), and as his mobility further deteriorated around the age of nine. An ongoing concern is that Sibling-O frequently elopes and demonstrates a diminished sense of fear. Parents and other caregivers must pay close attention to Sibling-O in public to ensure he does not run away. Sibling-O requires a one-on-one aide at school for safety and learning needs.

Sibling-Y has not forcefully pushed or bitten others. He has been less prone to elope and generally stays near his caregivers. Sibling-Y requires a one-on-one aide at school for learning and behavioral support needs.

Both siblings have been hyperactive and impulsive since early childhood. Around the age of seven, both siblings began taking medications for hyperactivity which have been helpful. They are both described by their parents as generally very happy and playful children.

3.1.4. Sleep

Around ages six and seven, Sibling-Y and Sibling-O began experiencing difficulties falling asleep and staying asleep through the night, respectively. However, Sibling-O experiences these difficulties more frequently than Sibling-Y. Since the age of seven, both siblings have been taking medications to help with sleep.

3.2. Sensory

3.2.1. Vision

Sibling-O has shown no signs of visual impairment while Sibling-Y was diagnosed with mild myopia at the age of four. Sibling-Y has a pair of prescription glasses, but he does not often wear them. His eyesight has remained stable over time.

3.2.2. Hearing

Audiometry revealed that Sibling-O had mild hearing loss on the right and normal hearing on the left at age five. His hearing has remained stable. Sibling-Y was found to have moderate to significant bilateral hearing loss at age four. He currently has hearing aids. Neither sibling has had recurring ear infections.

3.3. Dental

Tightness in Sibling-O's temporomandibular joint creates difficulty assisting him with brushing and flossing. By the age of five, Sibling-O had developed several cavities in his primary teeth, which were
filled. Furthermore, it has been difficult for Sibling-O to sit for dental exams due to his neurobehavioral symptoms; he requires specialty dental care with papoose restriction.

Sibling-Y’s temporomandibular joint is not restricted, improving access for brushing and flossing, and he has not developed any cavities. Sibling-Y tends to tolerate dental exams adequately; he sees a family dentist with adult assistance.

3.4. Swallowing

Sibling-O started to experience difficulties with swallowing at age 13. He sometimes coughs when he drinks clear liquids. By contrast, Sibling-Y has not experienced these difficulties with swallowing.

3.5. Pulmonary

Neither sibling has experienced significant airway obstruction, sleep apnea, snoring, or recurrent respiratory infections.

3.6. Cardiac

Longitudinal cardiac echo findings are presented in Table 1. There was a marked difference in valve appearance between Sibling-O and Sibling-Y on initial cardiac echoes. Sibling-O had mild thickening of both mitral and aortic valves while Sibling-Y had no thickening. Neither brother had valve regurgitation at initial echo. By about 10 years of age, Sibling-O had unmistakable thickening of both mitral and aortic valves and had developed mild aortic regurgitation. Sibling-Y had also developed aortic valve thickening and doming but there was no aortic insufficiency. Ventricular function (shortening fraction) was normal for both brothers at all time points where it was available. Neither sibling is prescribed any cardiac medications at this time.
Table 1
Summary of cardiac echo findings over time

<table>
<thead>
<tr>
<th>Cardiac Parameter</th>
<th>Sibling-O Age (years:months) – Assessment</th>
<th>Sibling-Y Age (years:months) – Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve thickening</td>
<td>• 3:9 – Mild</td>
<td>• 1:1 – None</td>
</tr>
<tr>
<td></td>
<td>• 10:1 – Thickened</td>
<td>• 9:8 – Mild</td>
</tr>
<tr>
<td>Mitral valve regurgitation</td>
<td>• 3:9 – None</td>
<td>• 1:1 – None</td>
</tr>
<tr>
<td></td>
<td>• 10:1 – Trace</td>
<td>• 9:8 – Trivial</td>
</tr>
<tr>
<td>Aortic valve thickening</td>
<td>• 3:9 – Mild</td>
<td>• 1:1 – None</td>
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<tr>
<td></td>
<td>• 10:1 – Thickened</td>
<td>• 9:8 – Thickened-doming</td>
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<tr>
<td>Aortic regurgitation</td>
<td>• 3:9 – None</td>
<td>• 1:1 – None</td>
</tr>
<tr>
<td></td>
<td>• 10:1 – Mild</td>
<td>• 9:8 – None</td>
</tr>
<tr>
<td>Shortening fraction</td>
<td>• 3:9 – 45.9</td>
<td>• 1:1 – 47.42</td>
</tr>
<tr>
<td></td>
<td>• 10:1 – 42.1</td>
<td>• 9:8 – Missing (report said ‘normal’)</td>
</tr>
</tbody>
</table>

3.7. Gastrointestinal

At the time of diagnosis, Sibling-O had an enlarged liver and spleen (palpable two fingerbreadths below the costal margin), with an abdominal ultrasound revealing hepatosplenomegaly with homogeneous echogenicity. After six months of ERT, the liver and spleen were no longer palpable.

Liver and spleen were not palpable at the time of Sibling-Y’s diagnosis and have remained as such.

Neither sibling has had inguinal hernias, nor gastrointestinal complications such as frequent vomiting, diarrhea, or constipation.

3.8. Musculoskeletal

Key musculoskeletal findings are presented over time also representing type of treatment, i.e., before standard intravenous ERT, before enrollment in IT idursulfase, and before Sibling-Y began the clinical trial of CNS-penetrant ERT (Figure 2).

3.8.1. Growth

Both siblings showed accelerated growth from birth to three years of age, and reached the 97th percentile for height and weight. Their height growth curves overlapped until the age of 10, with heights at the 97th percentile until six years of age (Fig. 3A). Growth velocity decreased thereafter, with heights measuring at the 90th percentile by 7.5 years of age. The growth velocities of the siblings diverged thereafter:
Sibling-O: By 10.5 years, his height measured at the 50th percentile. A pubertal growth spurt (8cm gain across 1 year, i.e., between 11 and 12 years old) was followed by rapid decrease in growth velocity after age 12 years. At the most recent measurement (age 13.5 years), height was 151.8 cm (25th percentile) and he was thought to be approaching his final adult height based on bone age at the time of 14 years.

Sibling-Y: By 9.5 years, height was at the 75th percentile. At the most recent measurement (age 10.5 years), determined to be prepubertal, height was 143 cm (50-75th percentile).

Both siblings’ weights were 97 percentile until 5 years old. Up to 8 years of age, the weight curves of both siblings showed a similar pattern (Fig. 3B).

3.8.2. Joint

Sibling-O was born with clenched hands, which took several weeks of physical therapy to release. During early childhood, upper extremity joints including shoulders, wrists, and fingers became more contracted, and increasingly stiffened, leading to clumsiness in fine motor skills. Although he started to walk independently at one year of age, he frequently used toe walking until the diagnosis was made. Established joint contractures remained stable or progressed over 10 years of ERT (Fig. 4A and 4C), resulting in restricted mobility. He has displayed more difficulties in walking in general. His mobility was characterized as following a constant slow decline since diagnosis. By age 10, independent walking distance shortened. By age 11, he started using an adaptive stroller outside when tired or when there are slopes along the path. At 13 years of age, he has significant contractures of shoulders, elbows, fingers, hips, knees and ankles; his walking distance is shortened to less than one mile.

Sibling-Y: There have been no significant joint contractures except mild contractures in shoulders at the time of diagnosis and initiation of ERT (Fig. 4B). At the most recent examination performed when he was 10.5 years, Sibling-Y could independently hike more than six miles with mild elevations and he had no functional limitations in using his joints despite mild contractures in shoulder and wrist joints (Fig. 4D). Sibling-Y was able to learn how to swim and bike, whereas his older brother was not.

3.8.3. Skeletal

At the time of diagnosis, Sibling-O had dysostosis multiplex including mild odontoid hypoplasia, inferiorly beaking vertebrae, and rounded iliac wings while Sibling-Y showed milder bone deformities in vertebrae and iliac bones. On skeletal survey at the age of 13, Sibling-O had skeletal deformities including beaking vertebral bodies without scoliosis or kyphosis, flattened femoral head with dysplastic acetabuli, genu valgum, and pes cavus. On skeletal survey at the age of 10, Sibling-Y had similar skeletal deformities but with milder degree of severity.

3.9. Laboratory

At diagnosis, urinary total GAGs were measured at abnormally high levels in both siblings. Urinary GAG levels were reduced early in the course of IV ERT and remained stable during ERT. Sibling-O’s urinary GAG levels were re-elevated after he stopped ERT (Fig. 5).
Sibling-O had measurable anti-IDS IgG antibodies 3 months after the initiation of ERT, which were undetectable after 2 years of ERT. Sibling-Y has not developed anti-IDS antibodies. After approximately 10 years on ERT, neither sibling has IDS-neutralizing antibodies or anti-IDS IgE antibodies.

3.10. Caregiving

3.10.1. Care Needs

Both siblings need help with daily living activities, although to varying degrees of required caregiver support, due to differences in mobility, neurocognitive function, and neurobehavioral symptoms.

Sibling-O has always required direct assistance with daily activities and tasks, such as washing and dressing. He has never been toilet trained, has always worn diapers, and requires assistance with toileting.

Sibling-Y can wash and dress himself with supervision, and he requires much less assistance than his brother. Sibling-Y is toilet trained.

3.10.2. Family’s Perception of Caregiving and Quality of Life

The siblings receive care primarily from their parents and sometimes from their grandparents. The parents reported that it can be difficult to provide care due to the siblings’ hyperactivity, impulsivity, sensory-seeking behaviors, and sleep difficulties. The siblings were described as “keeping the adults in the house very busy.” However, over the past two years, the parents have experienced less stress providing care for Sibling-O due to his reduced mobility. Nevertheless, Sibling-O still continues to require significant attention and care, particularly with toileting which necessitates physical maneuvering, calming, and support from multiple adults.

The family's perception of quality of life for the children is that Sibling-Y’s is superior, as his physical and mental capabilities offer him “a better chance of enjoying life.” Sibling-Y swims, bikes, and enjoys the outdoors more, and can play with puzzles (assembles 200-300 piece puzzles) and understand movies and stories for entertainment. He is able to enjoy independent movement and some independence in life activities. Sibling-O is much more restricted in his access to pleasurable activity, independent movement, and independence in life activities, thus limiting his free volition to fulfill his needs or desires on his own.

4. Discussion

We have chronicled the long-term outcomes, in system-by-system fashion, for a pair of siblings who began ERT for neuronopathic Hunter syndrome at different ages, because the diagnosis from clinical disease in the elder 3.7-year-old brother prompted diagnosis in the 12-month-old brother, who was minimally symptomatic. After nearly a decade of therapy, there were more severe and life-limiting disease manifestations for the elder-treated sibling (Sibling-O) in terms of skeletal/joint disease (with related limitations to mobility and basic dental care), and neurocognitive and neurobehavioral function. These
differences in disease progression were felt by the parents to have a profound effect on the boys’ quality of life, creating disparate experiences for the two boys, tied to the lag to starting ERT. The younger-treated brother, Sibling-Y, has “a better chance of enjoying life” due to his ability to engage in many classic childhood diversions such as biking, swimming, playing with puzzles, and understanding movies and stories, and to complete many tasks of daily living without the need for full hands-on adult assistance. By contrast, the elder-treated brother, Sibling-O, experiences disease-related barriers to all of these diversions as well as basic tasks of daily living due to his severely limited mobility and comprehension.

Findings of fewer and less severe disease manifestations in Sibling-Y align with a recent report that used statistical models to assess and to predict outcomes of ERT in patients from the Hunter Outcome Survey patient registry (NCT03292887); specifically, Muenzer and colleagues [23] found that predicted outcomes after 5-8 years of ERT were more favorable across all clinical parameters for patients who began ERT before age 18 months. Even prior to this report, a Delphi consensus recommended presymptomatic ERT for neuronopathic MPS II [24]. Further, the present study’s outcomes are consistent with two other MPS II studies reporting superior treatment response for a presymptomatically diagnosed sibling compared to a clinically diagnosed older sibling. One such case study reported 32-month outcomes of standard ERT in a sibling pair who began treatment at 3 years old and 4 months old, respectively: The younger-treated sibling was generally spared most of the somatic complications of Hunter syndrome seen when his older brother had been his same age, including joint contractures [25]. Dysostosis multiplex was evident in both siblings but much milder in the younger; neurocognitive function was impaired in the older treated brother, and slowly sloped downward from average to just below average in the younger treated brother. A more recent sibling case study involved prenatal diagnosis of one child following the diagnosis in a 2-year-old sibling, with standard ERT beginning at 1 month old and 2 years old, respectively [26]. The younger child was transitioned to a blood-brain barrier penetrating ERT at age 1 year 11 months whereas the elder remained on standard ERT. The two-year follow-up data suggest the younger had not developed any disease symptoms and maintained an average neurocognitive developmental trajectory, whereas the elder’s course involved several systemic manifestations of disease and neurocognitive impairments. In both of these case reports, the authors called for longer-term examination of outcomes.

Skeletal and joint disease are pervasive and difficult to address manifestations of Hunter syndrome. It has been noted that improvements in these areas could be reasonably assumed to improve function and quality of life in MPS II [19], and the present findings provide data to support these assumptions. Prevention of skeletal and connective tissue involvement of a patient with MPS I treated with ERT from birth [27] raises the possibility that the superior outcomes for Sibling-Y may have been even better, were ERT started before age 13 months.

Cardiac valvulopathy was recently found to have a higher incidence over a 10-year follow-up period than in previous reports [11]. In line with those findings, Sibling-O showed mild cardiac valve thickening at 3 years 9 months, but by 10 years of age developed unmistakable valve thickening of both valves and mild aortic regurgitation. By contrast, Sibling-Y showed no valve thickening at 13 months of age but mild thickening of the aortic valve, with neither regurgitation nor stenosis of the valve, over the ensuing 10
years. The cardiac findings seen in these brothers are subtle but lend support to the importance of early treatment in delaying the onset of, and possibly attenuating, cardiac valvulopathy in MPS II. Indeed, the only therapeutic approach to fully prevent difficult-to-address pathologies, such as cardiac disease, in large animal MPS models involved therapy from birth, such as in the canine model in MPS I [28]. With first echo and treatment at 13 months of age, Sibling-Y was already ‘old’ by standards for another MPS type, MPS I, which was added to the RUSP in 2016. Thanks to NBS, most children with severe MPS I would already have begun ERT within weeks of birth, and bone marrow transplantation within the first 6-9 months of life, if not earlier. Emerging evidence supports the concept of improved outcomes with early transplant for Hurler syndrome [29].

The potential for therapy from birth would be afforded by newborn screening for MPS II, which is under consideration for addition to the RUSP. MPS I was added to the RUSP in 2016, in large part due to the body of evidence demonstrating neurocognitive benefit of early hematopoietic stem cell transplant for the neuronopathic phenotype of MPS I, Hurler syndrome [30]. The present report aligns with this concept in similar pattern for MPS II, because when each brother was around 5 years old, Sibling-Y measured too neurocognitively high, and Sibling-O measured too low, to meet eligibility criteria for enrollment in a clinical trial (NCT02055118). Neurobehavioral impairments also differed, with the elder-treated brother showing substantially more physical behaviors including forcefully pushing others and biting, which were not exhibited by the younger-treated brother. Parent explanation of these behaviors as non-aggressive but rather sensory-seeking aligns with findings from a recent report of the multiple meanings behind the neurobehavioral features of this condition [4]. Both brothers, but to a more significant degree Sibling-O, display elopement behaviors, which are a cause of premature death due to drowning, traffic accident, and injury in pediatric populations with neurodevelopmental differences such as autism [31, 32]. The present study offers unexpected data suggesting neurocognitive and neurobehavioral benefit associated with earlier initiation of ERT for the neuronopathic phenotype of MPS II. While standard intravenous ERT is not expected to cross the blood-brain barrier, this pattern of better CNS functional status with early ERTs has been seen in MPS I, with speculation that general feelings of wellness and increased physical flexibility enabled more opportunities for learning and absorbing information without the burdensome distraction of intense pain, joint disease, and/or other disease symptoms [33, 34]. Additionally, there may be other aspects of systemic ERT that address aspects of CNS disease by as yet unrecognized mechanisms.

Regardless of the potential explanations for differences in neurocognitive and neurobehavioral signs, a significant problem with MPS II is that the prediction of phenotype is challenging for a larger segment of the MPS II population than for MPS I. In MPS II, phenotype based on genotype can be particularly unreliable, except in cases of previously characterized disease-causing alleles [35]. However, a lack of neurocognitive phenotype prediction does not actually create a significant quandary with respect to initiating ERT, as the present study demonstrated benefits distinct and independent from the benefits for neurocognitive and neurobehavioral function. Specifically, the differences in skeletal/joint disease (Fig. 3) and mobility have determined the types of activities that the boys may engage in, with far greater limits for the elder-treated boy. While the neurocognitive and neurobehavioral symptoms undoubtedly have a role in reducing the boys’ independence, it is not neurodegeneration underlying Sibling-O’s need for an
adaptive stroller, but rather severe multiple joint contractures and skeletal disease. Skeletal and other somatic disease manifestations are present regardless of phenotype and can be severe even in individuals with minimal neurocognitive effects [9–11], which is a meaningful point to consider when concerned about phenotype prediction.

While caregiver and family burden is incompletely characterized in MPS disorders [4, 6, 7, 36–38], the present report illustrates caregiver physical strain associated with the joint and mobility limitations experienced by Sibling-O, whose physical support needs require intensive and continual caregiver assistance throughout the day. This physical assistance for a growing child who loses mobility has been reported as a serious factor in caregiver burden in another neuronopathic MPS, Sanfilippo syndrome [37, 38]. Thus the physical complications, independent of neurocognitive or neurobehavioral outcome, may be implicated in “spillover effects” on caregiver health as the physical strain of caregiving is considerable, and there have been calls to conceptualize “health as a family affair” [39]. Information on the caregiver experience has been recognized by regulatory bodies as an important source of information on disease progression and response to treatment [40].

One limitation of the present report is the change in systemic therapies to include clinical trials of ERTs during the retrospective study period. Unchanged treatment with only FDA-approved therapy may have afforded a purer analysis of disease change over time, and could reduce doubt that some of Sibling-Y’s benefit was attributable to novel therapy rather than early intervention. However, benefit of pre-symptomatic treatment was already evident before enrollment in the first clinical trial, as seen by striking differences in joint disease (Fig. 3) and in neurocognitive function. With a number of novel therapies targeting CNS function currently approved outside the United States [41, 42], in trial (NCT04571970, NCT03566043, and NCT04251026), or in development, it is likely that the treatment picture for MPS II will soon be changing, but decisions about therapy-from-birth are still meaningfully and actionably informed by the current report and others [25, 26].

5. Conclusions

This report addresses questions previously posed in the literature, about whether the differential benefits of earlier initiation of therapy remain in the long-term. The data suggest persistently reduced severity and occurrence of symptoms for the younger treated sibling than the older, over a decade of treatment. An important contribution of the current study is the parent perspective on the lived experience of the children and the caregivers, which revealed significant benefits to the quality of life for the child and separately for the family, afforded by earlier initiation of therapy. Findings strengthen the argument for earlier treatment that would be enabled by newborn screening.

Declarations

Consent for publication was provided by the parent.
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Abbreviations

CNS, central nervous system;

DAS-II, Differential Ability Scales, Second Edition;

ERT, enzyme replacement therapy;

GAG, glycosaminoglycan;

HCT, hematopoietic cell transplantation;
IDS, iduronate-2-sulphatase;

IT, intrathecal;

MPS, mucopolysaccharidosis;

MPS II, mucopolysaccharidosis type II, Hunter syndrome;

MRI, magnetic resonance imaging;

NBS, newborn screening;

RUSP, Recommended Uniform Screening Panel

References


6. N. Grant, Sibling and family caregivers Bmj 362 (2018) k3158.


Figures

Figure 1

Neurocognitive and neurobehavioral symptom progression and systemic treatments This timeline depicts siblings’ ages of key functional symptom onset or change, as identified on medical exam or by caregiver observation. Timing of initiating therapies (and cessation, when applicable) is also represented. While
symptom onset and/or change is evident across both boys’ lives, the severity of symptoms and functional impairments is greater for Sibling-O (green).

**Figure 2**

Timeline of musculoskeletal findings and systemic treatments This timeline depicts siblings’ ages of key musculoskeletal symptom onset or change, as identified on medical exam or by caregiver observation. Timing of initiating therapies (and cessation, when applicable) is also represented. While symptom onset and/or change is evident across both boys’ lives, the severity of symptoms and functional impairments is greater for Sibling-O (green).
Figure 3

The siblings’ growth charts for height (A) and weight (B) Height growth curves for both boys overlapped until age 10, after which Sibling-O showed more deceleration of growth. Weight curves overlapped until age 8, after which Sibling-Y decreased in velocity of weight gain.
Comparison of joint progression over about a decade. Photographs of joint contractures of the hands, restricted shoulder range of motion, and pes cavus deformity for each sibling. Sibling-O’s joint disease is evident at age 4.3 years, i.e., about 6 months on ERT (A), including significantly restricted shoulder ROM preventing reach much above the browline. By contrast, Sibling-Y’s joint disease is more attenuated at age 1.5 years, i.e., also about 6 months on ERT (B), including the ability to reach above the head. After around a decade of therapy, Sibling-O at age 13 years (C) showed persistent contractures despite ERT. In comparison, Sibling-Y’s joint disease at age 11 years (D) showed no significant contractures except mild limitations in shoulders and hands. Photographs were provided by the parents and used with permission. ERT, enzyme replacement therapy.
Figure 5

Changes in total urinary GAGs since initiation of ERT. Total urinary GAGs are plotted against years since initiating treatment with ERT. Due to data availability, the first urinary GAG measurement for Sibling-O was obtained approximately 2 weeks after initiating ERT, and the first urinary GAG measurement for Sibling-Y was obtained before initiating ERT. After initiating ERT, urinary GAGs decreased in both siblings over a period of approximately 7 years. Around 11.7 years of age, Sibling-O experienced an increase in urinary GAGs after withdrawing from ERT and transitioning to palliative care due to progression of neurodegeneration. GAGs, glycosaminoglycans; ERT, enzyme replacement therapy.