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Original Research

Musculoskeletal health in Hunter disease (MPS II): ERT improves functional outcomes

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Abstract. Musculoskeletal disease is a significant burden for children with Mucopolysaccharide (MPS) disorders. The Pediatric Outcomes Data Collection Instrument (PODCI) is a validated, functional measure of musculoskeletal health in children with disabilities. The goal of this study is to describe the musculoskeletal manifestations of children with MPS II (Hunter syndrome), and their functional response to intravenous enzyme replacement therapy (ERT). Patients with MPS II were prospectively entered into an IRB approved registry. Chart review of physical findings including, shoulder, elbow, hip, knee and ankle range of motion, and need for carpal tunnel release was performed. Radiographs of the spine and pelvis were evaluated in all patients. Serial PODCI exams were administered to all patients. Seven patients, 5 receiving ERT, were included. Four patients had spinal deformities, seven had modest hip disease, and two required carpal tunnel release. PODCI scores were abnormally low in all domains, but significant improvements in PODCI scores were documented with enzyme replacement therapy. Spine and hip deformity are ubiquitous in MPS II, none of which have required surgical intervention, but require long term monitoring. Patients with MPS II should be monitored for carpal tunnel syndrome. Functional improvements are seen, as documented by the PODCI, in children with MPS II on ERT.

Keywords: Hunter syndrome, mucopolysaccharidosis, PODCI, hip, spine

1. Introduction

Hunter Syndrome (MPS II) is an X-linked, autosomal recessive form of mucopolysaccharidosis (MPS), caused by a deficiency in iduronidate-2-sulfatase (I2S), resulting abnormal accumulation of cellular glycosaminoglycans, heparin sulfate and dermatan sulfate [12,14]. Clinical manifestations of this disease process include developmental delay, hearing loss, upper airway obstruction, hepatosplenomegaly, valvular heart disease, stiff joints, short stature and skeletal deformities. Dysostosis multiplex, the constellation of skeletal abnormalities classically seen in MPS, results from defective endochondral and membranous bone formation throughout the body, including the hips, knees and spine [3,5,15]. The skeletal disease manifestations of MPS range from mild platyspondyly with or without epiphyseal dysplasia to severe, life-threatening spinal deformities and crippling hip deformities [8,11, 17]. Joint stiffness is associated with MPS II, compounding the problems associated with the skeletal deformities. Surprisingly, the musculoskeletal manifestations of dysostosis multiplex have not been detailed for Hunter Syndrome.

Intravenous enzyme replacement therapy (ERT) in the form of recombinant human I2S (idursulfase, Shire Human Genetic Therapies, Inc., Cambridge, MA) became commercially available in July 2006. Phase II/III studies of the effect of ERT in MPS II showed signifi-

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Table 1
Nominal data on seven subjects with MPS II

Patient #	Age at diagnosis	Age (yrs)	Disease severity	I2S enzyme activity (%)	Mutation	Height (cm)	ERT treatment (Y/N)	Duration ERT (mos)
1	4	13	severe	*	*	122.4	N	–
2	4	8	severe	*	*	106	N	–
3	3	16	attenuated	1.2	c.138C>A (p.D46E)	122.5	Y	24
4	2	14	severe	2.4	c.1048A>T (p.T350N)	116	Y	18
5	7	9	severe	"low"	c.1506G>C (p.502W)	119	Y	12
6	2	11	severe	1.9	c.629delA	117	Y	12
7	2	4	severe	0.07	c.240+1G>A	102	Y	12

$*$ = not documented.

cant improvements in 6-minute-walk time (6MWT) and measures of pulmonary function [13]. Acceleration of growth and reduction in joint stiffness has been demonstrated in human trials for other forms of MPS [7,9]. Animal studies have also demonstrated an alleviation of skeletal deformities in MPS VI cats [2].

Obtaining objective functional measurements in MPS remains a significant challenge, particularly in the subset of patients who are too medically frail to participate in surrogate measures of function such as the 6MWT. The Pediatric Outcomes Data Collection Instrument (PODCI) is a validated functional assessment tool developed for children with moderate to severe disabilities [4]. This assessment tool can be used in children aged 2 to 18 years, and administered either through the parent or directly to an adolescent capable of completing the exam. The results are reported in six domains: upper extremity, transfers and basic mobility, sports and physical functioning, comfort/pain, happiness with physical condition, and global function. The PODCI has been shown to have good reliability, construct validity, and sensitivity to change, and as such is ideal for monitoring musculoskeletal responses to medical and surgical interventions [1].

The objectives of this study are to 1) document musculoskeletal abnormalities in MPS II (Hunter Syndrome) and 2) document functional changes with ERT. We hypothesize that patients with MPS II have significant musculoskeletal disease, and that intravenous ERT improves function as measured by a validated instrument (PODCI).

2. Methods

This study represents data from an IRB approved registry of patients receiving care at a single institution. Seven patients with MPS II were identified. We performed a retrospective chart review of urine glycosaminoglycans (GAG), physical findings (shoulder, elbow, hip, knee and ankle range of motion), need for surgical interventions for musculoskeletal indications and evaluation for radiographs of the spine and pelvis.

For the five patients who elected to proceed with ERT, serial PODCI exams, including pretreatment assessments, were performed with a minimum of 1 year of enzyme therapy. The three versions of the PODCI instrument (Parent of Child, Parent of Adolescent and Adolescent; available online at http://www.aaos.org/research/outcomes/outcomes_peds.asp) were administered every three to six months. Questionnaires were collected by research staff and the results entered into an Excel (Microsoft) scoring spreadsheet also provided by the American Academy of Orthopaedic Surgeons website.

Descriptive analyses are presented for physical findings, radiographic findings and evaluation for surgical interventions. Statistical analysis of PODCI domain scores was performed using one tailed Wilcoxon signed rank test.

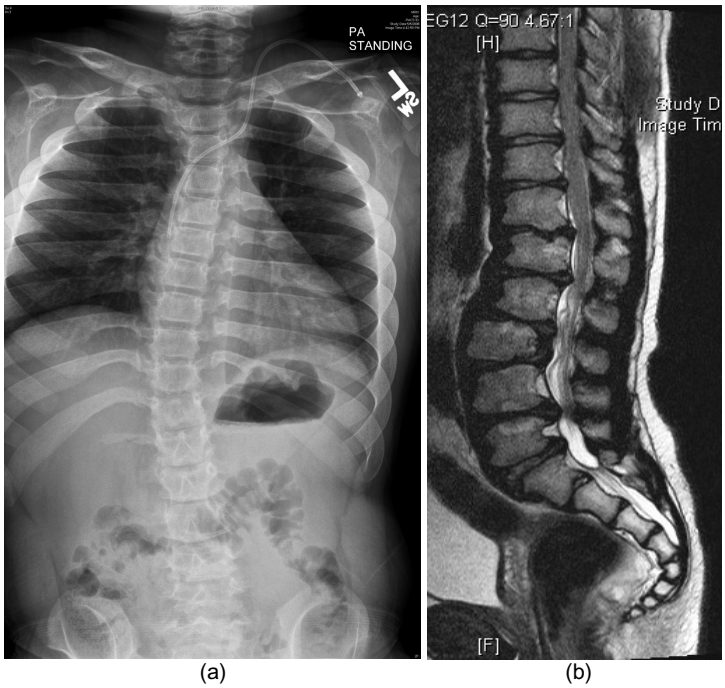
3. Results

In all, seven patients with Hunter Syndrome seen at our institution in the last 5 years were reviewed for this study. Patients' ages ranged from 4–16 years (Table 1). Chart review revealed that all seven patients had limited shoulder ROM, and that each patient also had some combination of limitation of motion in the elbow, hip, knee or ankle. (Table 2) Radiographic review of six of the seven patients identified four patients with spinal deformities. Two patients had scoliosis, one of which also had L3 spondylolisthesis and a corresponding anterior thigh radiculitis (Fig. 1). Two had "classic" thoracolumbar kyphosis secondary to anterior-superior vertebral body hypoplasia (Fig. 2). None of these patients have required surgical intervention at this time; however the one patient with scoliosis, spondylolisthesis and radiculitis is currently considering surgery. Pelvic

Table 2
Musculoskeletal findings with most recent range of motion data available

Patient #	Spine x/r	Hip x/r	Max shoulder FF/abd	Elbow ROM	Hip ROM	Max knee extension	Max ankle dorsiflexion	CTR (Y/N)
1	19 deg scoli	mild dysplasia	140	70–150	nl	nl	25	N
2	25 kyph	mild dysplasia	limited	limited	limited	–	–	N
3	33 deg kyph	mild dysplasia	limited	–	nl	nl	5	Y
4	nl	mild dysplasia	100	60–130	nl	−5	10	Y
5	14 deg scoli	mild dysplasia	150	full	nl	nl	15	N
6	19 deg scoli	mild dysplasia	140	70–150	nl	nl	25	N
7	25 kyph	mild dysplasia	limited	limited	limited	–	–	N

x/r = x-ray, FF/abd = forward flexion and abduction, ROM = range of motion, CTR = carpal tunnel release, nl = normal.



(a) (b)

Fig. 1. Images from patient #3: a) 33° scoliosis with courseness of the bones and widening of the ribs, b) magnetic resonance imaging demonstrates mild thoracolumbar kyphosis and typical anterior vertebral body deficiency seen in MPS.

radiographs obtained in the same six patients revealed mild hip dysplasia in all of these subjects, none of which have complaints of pain. The appearance of the hips in all of subjects were strikingly similar with caput valgum and mild femoral head uncoverage (Fig. 3).

Two patients required carpal tunnel release (patients #3 and #4). Patient #3 has relatively attenuated disease, who at 15 years of age developed gradual onset of median nerve neuropathy, despite receiving ERT for almost a year. At the time of evaluation he had almost no feeling in his right hand, thumb, index, and middle finger. Nerve conduction studies demonstrated findings consistent with diffuse peripheral neuropathy. Given the striking clinical evidence of carpal tunnel syndrome, a carpal tunnel release was recommended and performed, with good result. At one year postoperative, he had decreased numbness compared to his preoperative status. He also complained that his left hand had increasing numbness since the time of last follow-up. The pain would wake him up at night, and radiated into all fingers. He has subsequently undergone left sided carpal tunnel release two months prior to this report, without complication.

Patient #4 presented at age 14 years with “increasingly clumsy hands”. He had received ERT for more than a year and a half. His exam revealed atrophy of the thenar musculature consistent with bilateral carpal tunnel syndrome. In addition, there were abrasions on his hands that indicated decreased sensibility. There was no gross sensation to pinprick at the fingertips of

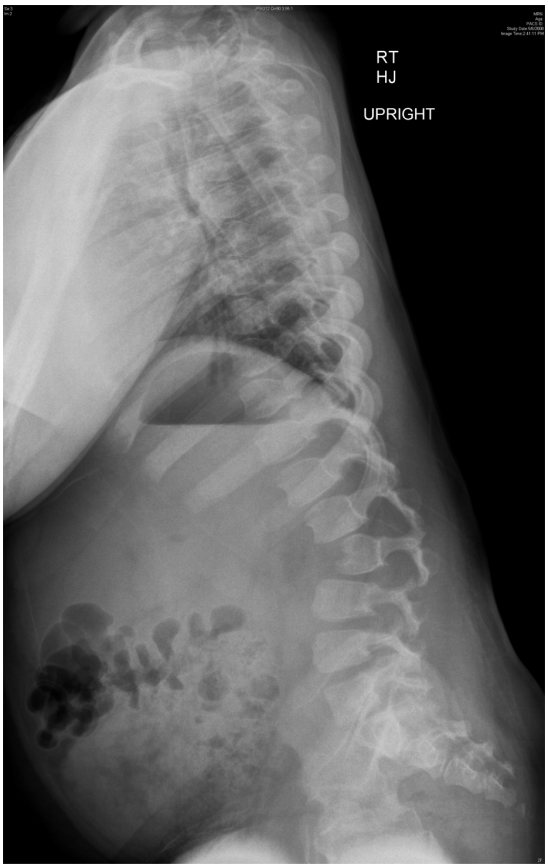


Fig. 2. Patient #7 was found to have a significant thoracolumbar kyphosis which is presently being observed for progression.

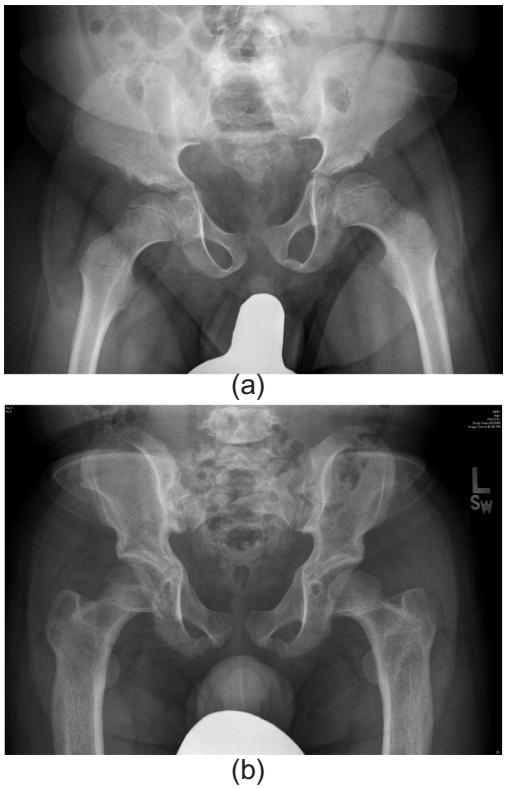


Fig. 3. Anteroposterior radiographs of patients #5 (a) and #3 (b). Note the valgus orientation of the proximal femoral epiphysis (caput valgum) and the relative lack of coverage by the actabuli. There does not appear to be any disease progression with skeletal maturation, and the hips typically remain asymptomatic with regard to subluxation.

the index and middle digits, while sensation appeared to be intact to pinprick at the ring and the small digits. This patient underwent bilateral carpal tunnel release without complication. He has subjectively done well with perceived improvement in his fine motor skills.

Five of the seven patients, aged 4 to 16 years, elected to proceed with treatment with ERT. All showed excellent response to therapy as indicated by a normalization of urine GAG excretion (Fig. 4). Functional assessment with the PODCI revealed statistically significant gains in three domains: transfers and basic mobility ($p = 0.04$), sports and physical functioning ($p = 0.03$), and global functioning ($p = 0.03$). Positive trends toward improvement were seen in the other three domains: upper extremity ($p = 0.15$), comfort/pain ($p = 0.11$) and happiness with physical condition ($p = 0.12$) (Fig. 5).

4. Discussion

Until now there has been no systematic review of the musculoskeletal manifestations of Hunter Syndrome (MPS II) despite the knowledge that skeletal manifestations in MPS can lead to significant morbidity. Deformities of the hip and spine are typically the most incapacitating and functionally limiting skeletal problems in MPS. These are also the anatomical sites in which surgical intervention can provide significant benefit. As such we chose to focus on these aspects for our radiographic review. Spine and hip anomalies were ubiquitous in this patient group. None, however, required surgical intervention, but certainly will require long term monitoring. It should also be noted that Madelung's deformity of the forearm is well acknowledged in MPS II, but does not lead to significant morbidity, nor is it amenable to surgical intervention [10]. As such, we did not focus on this entity. It should be noted that the one forearm radiograph obtained in this patient group did demonstrate a Madelung's deformity.

As a result of soft tissue deposition in adjacent tenosynovium, median nerve compression neuropathy and resultant carpal tunnel syndrome is common in the MPS disorders [6,16,18]. Two patients in this study

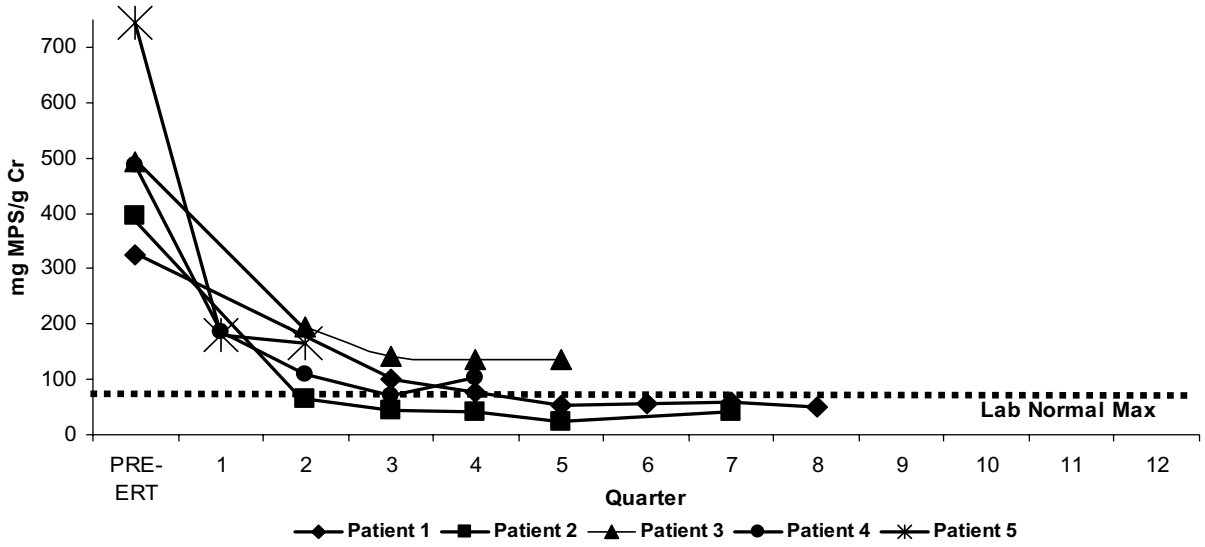


Fig. 4. Urine glycosaminoglycan levels show an excellent response to intravenous enzyme replacement therapy in all five patients treated.

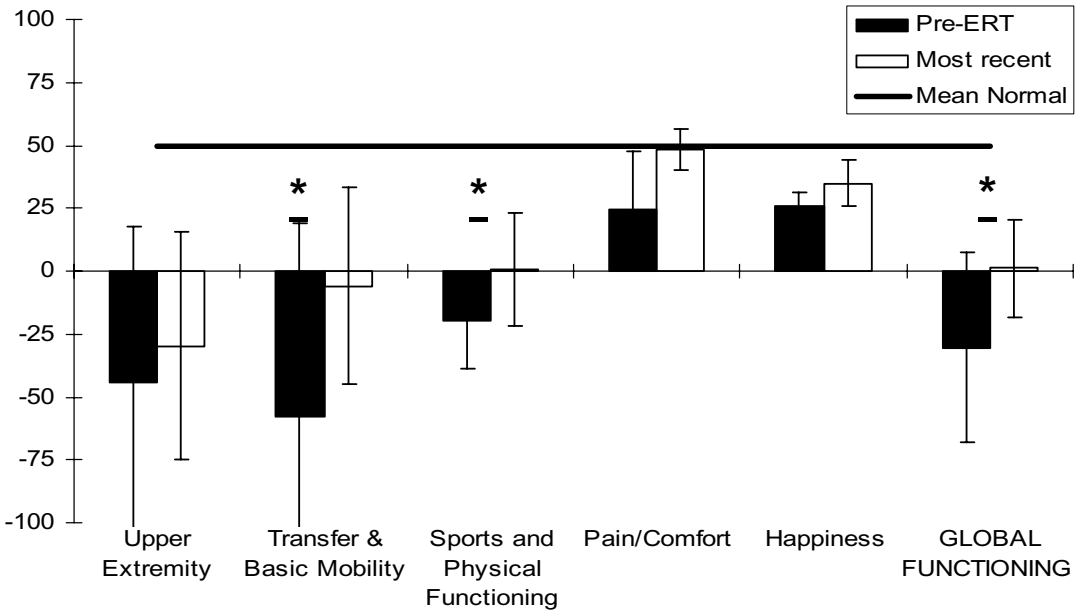


Fig. 5. PODCI scores ($n = 5$) improved in all domains with statistically significant improvements (* symbolizes $p < 0.05$) in transfers and basic mobility ($p = 0.04$), sports and physical functioning ($p = 0.04$), and global functioning ($p = 0.04$). Data are shown as mean values and standard deviation for each domain.

developed carpal tunnel syndrome more than a year after initiating ERT. Diagnosis of carpal tunnel syndrome in MPS can often be confounded by patients' developmental delays. Van Heest et al. have recommended routine monitoring via electrodiagnostic studies in MPS patients. In this group, diagnosis and the decision to recommend surgery was made in both patients by clinical signs and symptoms. Nerve conduction studies were obtained in one patient with minimal developmental delay, however the results were difficult to interpret as the findings were not classic for a compression neuropathy, but in fact more consistent with neuronal axon disease. Nonetheless, both patients seemed to do well with carpal tunnel release, with subjective improvements in function. The long term effect of ERT on the incidence of carpal tunnel syndrome and the ef-

fect of early intervention are unknown. Consequently, we recommend diligent clinical and, when possible, electrodiagnostic monitoring of all patients with Hunter Syndrome who are receiving ERT.

Functional improvements were seen in all domains of the PODCI in MPS II after the initiation of ERT, some reaching statistical significance even in this small group with clinical heterogeneity and short period of follow-up. Individually, each patient on ERT showed gains in one or more domains of their PODCI scores. As a group, domain findings were statistically significant for transfers and basic mobility, sports and physical functioning, and global functioning. The remaining three domains all showed strong statistical trends toward improvement. While not all of these gains can be attributed directly to improvement in musculoskeletal function, many can. We suspect that the improvements seen are likely attributable to improved muscle function and indirectly due to improvement in cardiovascular function.

The PODCI is as effective in measuring changes in our more severely affected patients (developmental delay and minimal ambulatory potential), as it is in those with a more attenuated presentation [1]. The sensitivity of the PODCI and its applicability to a broad range of pediatric patients makes it an ideal monitoring tool of functionality in the complicated and heterogeneous MPS patient population. There are many advantages to using the PODCI. The PODCI provides a very broad representation of function, thereby giving a "complete picture" of response to therapy. We also find that the PODCI helps families articulate the subjective changes they are seeing in their children. Another positive attribute is that the PODCI instrument and its scoring tool are freely available online. And finally, it is relatively easy to administer. Each administration takes our staff approximately 10–15 minutes, and can be performed through the mail when necessary.

Despite the encouraging findings of this study, significant study limitations associated with this rare patient population exist. Obviously, the number of patients is small, and patients with Hunter Syndrome represent a very heterogeneous population. Some of our patients were attenuated in terms of somatic and neurocognitive function. We had patients who at the onset of monitoring were unable to ambulate independently or were severely developmentally delayed. On the other end of the disease severity spectrum, this study includes a teenage boy who is in mainstream high school and requires minimal assistance with schooling and physical function. There is also a large range in the age of the patients, and therefore a broad range in the age at initiation of ERT. Finally, the duration of follow-up is limited to a minimum of one year with maximum duration of follow-up being two years.

In conclusion, spine and hip anomalies are ubiquitous in MPS II. None of these patients have required surgical intervention for these deformities, but will require long term monitoring. Patients with MPS II should be monitored for carpal tunnel syndrome, as they may require carpal tunnel release, despite treatment with ERT. Functional improvements are seen in all domains of the PODCI in children with MPS II on ERT. The PODCI is free, validated, easy to administer, and provides a global assessment of function in children of all physical abilities. It can be used for a single time point evaluation or for serial administrations over time, with or without an intervention. Consequently, we feel that the PODCI represents an ideal monitoring tool for pediatric patients with MPS.

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Conflict of interest

Klane White has received honoraria for educational lectures from BioMarin Pharmaceutical Inc., and Shire plc. Susan Hale and Michael Goldberg have no conflicts of interest to report.

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