Hip Dysplasia in Patients With Hurler Syndrome (Mucopolysaccharidosis Type 1H)

Dinesh P. Thawrani, MD, Kevin Walker, MD,* Lynda E. Polgreen, MD, MS,† Jakub Tolar, MD, PhD,‡ and Paul J. Orchard, MD‡*

Background: Hip dysplasia is common in patients with Hurler syndrome (HS). However, its prevalence and optimal management is not yet clear because of the rarity of the disease and the prior short life span of these patients. Recent advances in the management of these children using allogeneic hematopoietic cell transplant (HCT) has significantly increased their life expectancy, with many surviving into adulthood. This review was conducted to describe the experience of a single center with hip dysplasia in HS after HCT.

Methods: We performed a retrospective review of hip dysplasia in a consecutive series of patients with HS treated with HCT from 1985 to 2008.

Results: At 4.5 (± 2.9) years after HCT all 51 children (102 hips) with HS showed acetabular dysplasia and proximal femur valgus deformity. Mean age at HCT was 1.6 ± 0.9 years. Forty hips (39%) underwent hip reconstructive osteotomies at mean age of 6.8 ± 3.1 years. Significant radiographic improvement was noted in all radiographic parameters at 5.4 ± 3.7 years after hip surgery ($P < 0.001$). Acetabular index improved from 33.3 degrees (± 7.9) preoperative to 24.7 degrees (± 8) after surgery, lateral center edge angle improved from −5.3 degrees (± 10.9) to 35.2 degrees (± 17.8), migration index from 50.7% (± 15.7) to 9.6% (± 13.6), and femoral-neck-shaft angle from 150.9 degrees (± 5.8) to 130.8 degrees (± 12.4). Ten of the 40 hips underwent only proximal femoral varus derotation osteotomy and 30 underwent combined proximal femoral varus derotation osteotomy + pelvic osteotomy.

Conclusions: This study reports high prevalence of hip dysplasia (100%) in patients with HS. As significant radiographic improvement was achieved in those patients treated with surgical interventions we recommend annual orthopaedic evaluation of hips in patients with HS after HCT and intervention with reconstructive femoral and pelvic osteotomies for their hip dysplasia.

Level of Evidence: Level III.

From the *Department Pediatric Orthopedics, Gillette Children's Specialty Healthcare, St Paul; †Division of Endocrinology; and ‡Program in Blood and Marrow Transplantation, Department of Pediatrics, University of Minnesota School of Medicine, Minneapolis, MN.

J.T. and P.J.O. contributed equally.
There was no external source of funding for this study.
The authors declare no conflict of interest.

Reprints: Dinesh P. Thawrani, MD, Department of Pediatric Orthopedics, Gillette Children's Specialty Healthcare, 200 E University Avenue, St Paul, MN 55101. E-mail: dr_dineshthawrani@yahoo.co.in.

Key Words: Hurler syndrome, MPS-1, hip dysplasia, proximal femur osteotomy, pelvic osteotomy

(*J Pediatr Orthop* 2013;33:635–643)

Hurler syndrome (HS) is an autosomal recessive lysosomal storage disease, also called mucopolysaccharidosis type 1H with an estimated incidence between 0.61 and 1.3 per 100,000 live births.[1–3] The disorder is characterized by the deficiency of enzyme α-L-iduronidase (IDUA). Because of the lack of IDUA activity, accumulation of glycosaminoglycans (GAG) is observed. Patients with HS are unable to degrade dermatan sulfate and heparin sulfate. Accumulation of these products within lysosomes leads to multiorgan dysfunction and tissue damage.[4]

Historically, treatment of patients with HS was palliative and symptom based, predominantly because of their limited life expectancy, multisystem involvement, and severe cognitive impairment. However, recent treatment with allogeneic hematopoietic cell transplantation (HCT) has significantly improved the clinical manifestations of the disorder, and overall life expectancy.[2–4] After engraftment of allogeneic hematopoietic cells, an improvement has been noted in obstructive airway symptoms, hepatosplenomegaly, corneal clouding, hydrocephalus, hearing, and neurocognitive function.[2,5,6] The risk of heart failure and tachyarrhythmia is eliminated by 1 year after successful HCT.[2,7] The mean survival of children with HS treated with HCT has been reported to be 15.6 years, which is considerably higher than 6.6 years in children without HCT.[3] After HCT, the probability of survival has been high, 68%, 66%, and 64% at 1, 5, and 10 years, respectively.[3] Despite these improvements in survival and comorbidities, the myriad of musculoskeletal manifestations of HS symptoms seen in these patients (termed *dysostosis multiplex*) is less responsive to the treatment with HCT.[2,8,9]

Musculoskeletal manifestations of HS includes short stature, thickened calvarium, odontoid hypoplasia, atlanto-axial subluxation, localized thoracolumbar kyphosis, small clavicles, broad scapulas, acetabular dysplasia, coxa-valga evolving into hip subluxation, genu valgum, carpal tunnel syndrome, trigger finger, limited joint mobility, and soft tissue contractures. These skeletal abnormalities are thought to result from the combination of lack of skeletal remodeling, disordered endochondral and intramembranous ossification, focal failure of ossification, and infiltration of GAG into ligaments, tendons, joint capsules, and other soft tissue structures.[9–11] HCT has been reported to result in mild improvement in joint mobility, facial features, and longitudinal growth. Unfortunately, HCT has not been shown to have a positive effect on the progression of kyphosis, genu valgum, and hip dysplasia.[10–12] Histological study of the growth plate in HS reveals a disruption in the programmed maturation of the chondrocytes leading to marked irregularities in cellular orientation. This disruption of the normal columnar architecture produces a relative barrier to the transport of diffusible corrective enzymes within the growth plate and is the presumed reason for the poor musculoskeletal response to the HCT.[2,9]

Although hip dysplasia is common in patients with HS its prevalence and management has not been adequately characterized.[10–13] Our institution is a referral center and leader in the treatment of patients with lysosomal storage diseases. As a part of our multidisciplinary approach, patients with HS are evaluated by an orthopaedic surgeon at the time of their initial visit and are then subsequently followed on an annual basis. The purpose of this study was to determine the prevalence of hip dysplasia in patients with HS after HCT and to evaluate the results after orthopaedic interventions used in their treatment.

METHODS

This is an institutional review board approved retrospective review of a consecutive series of patients with HS treated with HCT from 1985 through 2008 at our institution. Fifty-nine patients (118 hips) who survived more than a year after HCT were assessed for inclusion in this study. Eight patients (16 hips) were excluded because of inadequate or missing pelvic radiographs. The remaining 51 patients (102 hips) were analyzed for the current study, and were divided into 2 groups; a group that underwent surgery and a nonsurgery group. The surgery group was further divided into 2 subgroups depending on the type of surgery, those treated by isolated proximal femoral varus derotation osteotomy (P-FVDO), or combined P-FVDO and pelvic osteotomy (PO) (Fig. 1).

Radiographic evaluation of each hip was performed on supine anteroposterior pelvic radiographs with hips in neutral rotation. For hips in the surgery group radiographs at 3 different time points (immediate preoperative, postoperative, and most recent follow-up) were evaluated. Measurements were compared at each time point to the preoperative parameters. For hips in the nonsurgery group, the most recent available pelvic radiographs were evaluated. To minimize interobserver variation, all measurements were performed by a single physician. Hip dysplasia was quantified by the acetabular index of weight bearing zone (AI-WBZ, normal <20 degrees),[14] the lateral center edge angle (LCEA, normal >25 degrees) of Wiberg,[14] and the head migration index (MI, normal $<25\%$).[15] Coxa-valga was assessed by proximal femoral-neck-shaft angle (FNSA).

Clinical and operative records were reviewed to collect the following demographic and operative data: age at the time of HCT, age at the time of hip surgery, gender, side of surgery, type of surgery, estimated blood loss (EBL), time duration of the surgery, and intraoperative as well as postoperative complications. Procedures performed concomitantly with hip surgery and those performed subsequent to the index surgery were also recorded.

Statistical Methods

Quantitative variables are described by mean and SD (mean ± SD). The χ^2 test was used to compare categorical variables and Wilcoxon rank sum test to compare continuous variables for preoperative and most recent outcome groups. Similar tests were applied to compare 2 groups (surgical vs. nonsurgical) and 2 surgical subgroups (P-FVDO vs. combined P-FVDO + PO). A *P*-value of <0.05 was considered as statistically significant. All statistical analyses were performed with Statistical Analysis System (SAS) statistical software version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

There were 102 hips included in this analysis of 51 patients (29 males and 22 females). The average age at the time of HCT was 1.6 (± 0.9) years and average age at the time of this radiographic review for all 51 patients in this study was 6.12 (± 3.8) years. Acetabular dysplasia was noted in all hips, with mean AI-WBZ 32.5 degrees (± 7.7); LCEA −3.1 degrees (± 11.9); MI 51% (± 15.3). Proximal femoral valgus deformity was also common with a mean FNSA of 149.9 degrees (± 6.8).

Forty hips (39.2%) in 20 patients (12 males and 8 females) underwent hip reconstructive osteotomies. All 20 patients underwent bilateral hip surgeries, performed at the same time by 2 separate surgical teams. The average age at the time of hip surgery was 6.8 (± 3.1) years, an average of 5.1 (± 2.9) years after their HCT. The average body mass index at the time of surgery was 18.2 ± 2 (height 105.8 ± 14 cm and weight 20.8 ± 6.5 kg). Preoperative radiographs in the surgical group showed severe acetabular dysplasia with mean AI-WBZ 33.3 degrees (± 7.9); LCEA −5.3 degrees (± 10.9); MI 50.7% (± 15.7); and proximal femoral valgus deformity with mean FNSA 150.9 degrees (± 5.8) (Table 1).

Of the 40 hips in the surgery group, 10 hips in 5 patients underwent only P-FVDO at an average age of 6.5 (± 3.2) years (Fig. 1). Mean EBL was 147.5 ± 102.5 mL and mean total surgical time duration was 386 ± 26.9 minutes. Both sides were performed at the same time in all patients, thus EBL and time specified includes both sides as well as associated procedures performed (proximal medial tibial hemiepiphysiodesis in 2 knees). Average follow-up of this group was 34.8 (± 20.4) months after surgery. Proximal femoral valgus deformity was significantly improved by P-FVDO, and this improvement was maintained until most recent follow-up (Table 2). However, radiographic parameters specific to acetabular dysplasia (AI-WBZ, LCEA) were not changed and

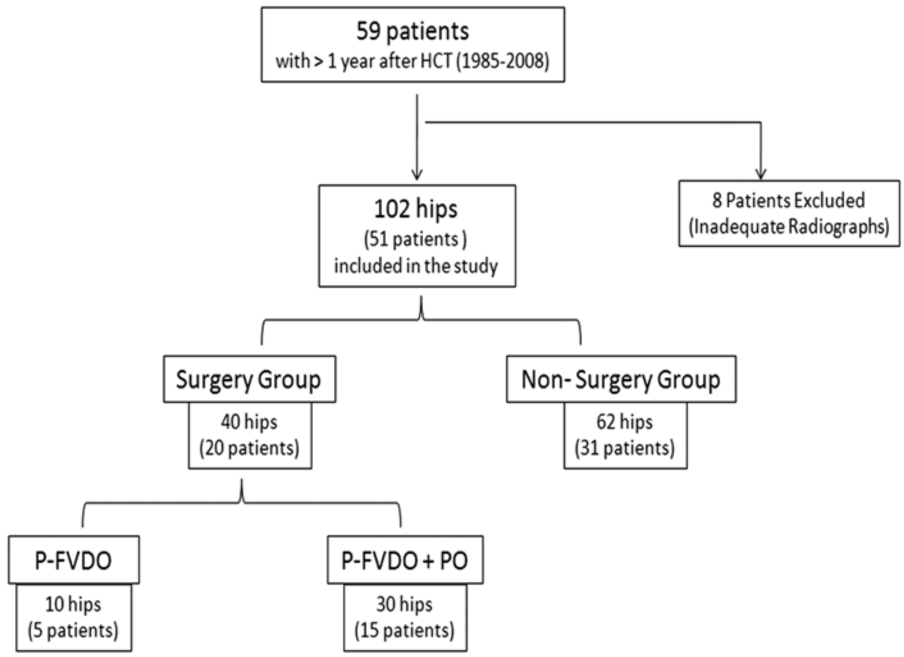

FIGURE 1. Flow sheet showing various groups and subgroups in the study. P-FVDO indicates proximal femoral varus derotation osteotomy; PO, pelvic osteotomy.

showed no remodeling of the acetabulum over time as evident on most recent follow-up radiographs (Table 2).

Remaining 30 hips in surgical group were treated with combined P-FVDO + PO at an average age of 6.9 (± 3.1) years (Fig. 1). Mean EBL was 357.3 ± 213.9 mL and mean surgical time duration was 284.1 ± 56.6 minutes. Both sides were performed at the same time in all patients, thus EBL and time specified reflects both sides as well as associated procedures performed. Associated surgeries were: proximal medial tibial hemiepiphysiodesis (n = 11), staple removal from proximal tibia (n = 3), claw toe correction (n = 2), adductor release (n = 1), and carpal tunnel release (n = 2). Postoperative radiographs showed significant improvement in all radiographic parameters. This improvement was maintained on most recent follow-up radiographs (Table 3). The average length of follow-up of this group was 6.3 (± 3.9) years after surgery. There were combination of different types of pelvic procedures performed including Pemberton (n = 15), Shelf (n = 12), and Dega (n = 3). There was no statistical difference in the radiographic outcomes depending on the type of PO performed.

Comparison of preoperative radiographic measurements showed no statistical difference between the groups that underwent only P-FVDO and those that were treated with combined P-FVDO and PO (Table 4). Immediate postoperative radiographs showed statistically better AI-WBZ in hips which underwent combined P-FVDO and PO than those which underwent isolated P-FVDO ($P = 0.04$). Most recent postoperative time of these 2 groups shows statistically different follow-up time period ($P = 0.01$) making groups unmatchable for comparison of their radiographic outcomes (Table 4).

There were 62 hips (31 right and 31 left) in 31 patients (17 males and 14 females) in the nonsurgery group. All these hips also had acetabular dysplasia with mean AI-WBZ 31.9 degrees (± 7.6); LCEA −1.7 degrees (± 12.5); MI 51.2% (± 15.3); and proximal femoral valgus deformity with mean FNSA 149.3 degrees (± 7.5). The average age at the time of this radiographic measurement

TABLE 1. Radiographic Findings at 3 Different Times of All Hips Underwent Reconstructive Surgery

	Pre-Op (P)	Immediate Post-Op (I)	Most Recent (R)	*P* (From P to R Time Point)
No. hips	40	40	37	—
Time from surgery (mo)	−0.6 (± 1.5)	7.4 (± 27.4)	64.9 (± 45.5)	< 0.01*
AI-WBZ	33.3 (± 7.9)	24.2 (± 8.7)	24.7 (± 8)	< 0.01*
LCEA	−5.3 (± 10.9)	30.4 (± 25)	35.2 (± 17.8)	< 0.01*
Migration (%)	50.7 (± 15.7)	12.4 (± 15.1)	9.6 (± 13.6)	< 0.01*
FNSA	150.9 (± 5.8)	129 (± 12)	130.8 (± 12.4)	< 0.01*

**P*-value < 0.05 is considered as statistically significant.
AI-WBZ indicates acetabular index of weight bearing zone; LCEA, lateral center edge angle, FNSA, femoral-neck-shaft angle.

TABLE 2. Radiographic Findings at 3 Different Times of Hips That Were Treated With Only Proximal Femoral Varus Derotation Osteotomy

	Pre-Op (P)	Immediate Post-Op (I)	Most Recent (R)	*P* (From P to R Time Point)
No. hips	10	10	10	—
Time from surgery (mo)	−2.3 (± 2.2)	0.2 (± 0.3)	34.8 (± 20.4)	—
AI-WBZ	32.6 (± 5.5)	28.9 (± 11.2)	27.3 (± 9.3)	0.13
LCEA	−3.5 (± 8.3)	5.9 (± 14.8)	−4.1 (± 13.1)	0.14
Migration (%)	49.5 (± 12.3)	38.1 (± 26.8)	39.4 (± 20.3)	0.20
FNSA	149.8 (± 7.5)	124 (± 13)	134 (± 8.1)	< 0.01*

**P*-value < 0.05 is considered as statistically significant.
AI-WBZ indicates acetabular index of weight bearing zone; LCEA, lateral center edge angle, FNSA, femoral-neck-shaft angle.

was 5.7 (± 4.1) years. This was not significantly different from the average age of patients who underwent hip surgery (6.8 ± 3.1 y) in the surgical group ($P = 0.17$). Severity of the acetabular dysplasia and proximal femoral valgus deformity were not statistically different between the 2 groups (nonsurgery group and preoperative measurements of surgery group) (Table 5).

The mean age of patients at the time of most recent follow-up in the surgical group, after surgery, was 12.0 (± 4.8) years (range, 5.4 to 21.2 y). In order to match patients with similar age range in the nonsurgical group, we excluded patients below 5.4 years of age from nonsurgical group, for a comparative analysis. After this exclusion, there were 28 hips in the nonsurgical group with age range 5.6 to 19.9 years at the time of radiographic assessment. These 2 comparable demographic groups, with and without surgery were radiographically analyzed for hip dysplasia. Acetabular dysplasia and proximal femoral valgus deformity were significantly worse in patients who did not undergo hip surgery compared with the hips of patients, at the same age range, but who have had hip surgery in the past (Table 6).

Comparison of hips in patients who underwent surgery at the age below 5 years or above 5 years showed no statistical difference in final outcomes as evident from their most recent follow-up radiographs except in their neck-shaft angle (Table 7). Hips in patients who underwent surgery at an early age (< 5 y) showed recurrence of their femoral valgus deformity over time in comparison with those patients who underwent surgery at later age (>5 y).

Revision Surgery/Complications

Two hips underwent revision surgery. One hip needed revision P-FVDO for persisting valgus deformity. This was performed 17 months after the index hip surgery (combined P-FVDO + PO). A second hip underwent revision P-FVDO as well as PO at the age of 12 years, 7.5 years after the index hip surgery (combined P-FVDO + PO).

One female patient developed slipped capital femoral epiphysis of left hip, 4.6 years after index hip surgery (combined P-FVDO + PO). Her body mass index was 18.8 and she was on growth hormone. She had a stable, chronic slipped capital femoral epiphysis, which was treated conservatively. Four years later she underwent a proximal femoral varus-flexion-derotation and shortening osteotomy at the intertrochanteric level for her residual hip deformity. Two months after this, she had implant loosening and underwent revision surgery and she subsequently healed her osteotomy.

In addition, 5 of 102 hips developed severe osteoarthritis (OA) warranting total hip arthroplasty. Three hips were from the surgical group and 2 from the nonsurgical group. All 3 from the surgical group have had combined P-FVDO + PO. One hip was treated with P-FVDO + PO at 14.8 years of age, which was higher than the mean age at the time of hip surgery in our study population (6.8 ± 3.1 y). The remaining 2 hips with severe OA underwent their index hip surgery (P-FVDO + PO) at 6.6 years of age.

Two hips with severe OA in the nonsurgical group were in the same patient. Radiographs analyzed in this patient were performed at 19.9 years of age, which was

TABLE 3. Radiographic Findings at 3 Different Times of Hips That Were Treated With Combined Proximal Femoral Varus Derotation Osteotomy and Pelvic Osteotomy

	Pre-Op (P)	Immediate Post-Op (I)	Most Recent (R)	*P* (From P to R Time Point)
No. hips	30	30	27	—
Time from surgery (mo)	0.0 (± 0.2)	9.8 (± 22.6)	76.0 (± 47.5)	0.00*
AI-WBZ	33.5 (± 8.6)	22.6 (± 7.2)	23.6 (± 7.3)	< 0.01*
LCEA	−5.9 (± 11.7)	14.6 (± 14.8)	11.8 (± 13.5)	< 0.01*
Migration (%)	51 (± 16.8)	27.8 (± 24.4)	33.5 (± 16.8)	< 0.01*
FNSA	151.3 (± 5.3)	130.3 (± 11.5)	129.6 (± 13.5)	< 0.01*

**P*-value < 0.05 is considered as statistically significant.
AI-WBZ indicates acetabular index of weight bearing zone; LCEA, lateral center edge angle; FNSA, femoral-neck-shaft angle.

TABLE 4. Comparison of Radiographic Measurements Between 2 Surgical Subgroups; Those Underwent Only P-FVDO and Those Underwent Combined P-FVDO+PO

	P-FVDO	P-FVDO + PO	P
No. hips	10	30	—
Age at HCT	1.5 (± 0.6)	1.7 (± 1.3)	0.59
Age at surgery	6.5 (± 3.2)	6.9 (± 3.1)	0.74
Time from HCT	5 (± 2.8)	5.1 (± 3)	0.88
BMI	16.8 (± 2.7)	18.3 (± 2)	0.18
Preoperative			
AI-WBZ	32.6 (± 5.5)	33.5 (± 8.6)	0.75
LCEA	−3.5 (± 8.3)	−5.9 (± 11.7)	0.55
Migration (%)	49.5 (± 12.3)	51 (± 16.8)	0.78
FNSA	149.8 (± 7.5)	151.3 (± 5.3)	0.49
Immediate postoperation			
AI-WBZ	28.9 (± 11.2)	22.6 (± 7.2)	0.04*
LCEA	5.9 (± 14.8)	14.6 (± 14.8)	0.16
Migration (%)	38.1 (± 26.8)	27.8 (± 24.4)	0.26
FNSA	124 (± 13)	130.3 (± 11.5)	0.19
Recent follow-up			
Age at recent x-ray	9.4 (± 3.4)	13.0 (± 4.9)	0.04*
Time from surgery (mo)	34.8 (± 20.4)	76.0 (± 47.5)	0.01*
AI-WBZ	27.3 (± 9.3)	23.6 (± 7.3)	†
LCEA	4.1 (± 13.1)	11.8 (± 13.5)	†
Migration (%)	39.4 (± 20.3)	33.5 (± 16.8)	†
FNSA	134 (± 8.1)	129.6 (± 13.5)	†

*P-value <0.05 is considered as statistically significant.

†Statistically different follow-up time period ($P = 0.01$) makes these group unmatchable to do further comparison of their radiographic outcomes.

AI-WBZ indicates acetabular index of weight bearing zone; BMI, body mass index; HCT, hematopoietic cell transplant; LCEA, lateral center edge angle; FNSA, femoral-neck-shaft angle; P-FVDO, proximal femoral varus derotation osteotomy; PO, pelvic osteotomy.

again significantly higher than the mean age of patients (5.7 ± 4.1 y) at which radiographs were analyzed in this study. Considering the low percentage of hips (5/102 hips, 4.9%) that were shown to have severe hip degeneration, we were unable to obtain any statistically significant predicting factors for the severe hip degeneration.

DISCUSSION

This radiographic study shows that all patients with HS developed acetabular dysplasia and proximal femoral valgus deformity even after receiving HCT during infancy. Those who underwent surgical intervention showed significantly better results at 5.4 years after surgery when compared with those who did not undergo surgery at a comparable age range (P-value <0.05, Table 6). In addition, acetabular coverage improved after combined P-FVDO + PO and was maintained until recent follow-up (~6 y), as opposed to those hips that underwent isolated P-FVDO and showed no radiographic remodeling of the acetabulum overtime.

HCT performed in patients with HS at an early age often results in near normal intellect and independent mobility beyond first decade of life.[2,3,11] In general, the first year after HCT is considered the time of highest risk of transplant-related morbidity and mortality. We believe elective hip surgery should be avoided during this time period if possible. One year after HCT, the probability of survival rate of patients is essentially the same at 5 and 10 years after HCT (~65%).[3] In the current study comparison of hips in patients who underwent surgery at an age below 5 years (≤4 y from HCT) compared with above 5 years, there was no statistical difference in final results except in their neck-shaft angle (Table 7). Hips in patients who underwent surgery at age under 5 years had recurrence of their femoral valgus deformity over time. There is no standardized optimal time for hip reconstructive surgery, but it is postulated that surgery performed at an early age may preserve hip motion and prevent later sequelae of hip subluxation, most notably degenerative joint disease leading to severe OA. Weisstein et al[10] reported that 6 of their 7 patients needed surgery at 4.8 years of average age because of worsening hip dysplasia. Similarly, in the current study the average age at the time of hip osteotomies was 6.8 (± 3.1) years, which was 5.1 (± 2.9) years after HCT. This is the common age of preference for hip surgery by surgeons because of various anecdotal reasons, such as it gives enough time to recover from HCT and address some other essential health issues such as cardiac, respiratory, or sometimes spine before elective hip reconstruction, give tolerable age for long anesthesia period, adequate size, and ossification of bones to perform a desired osteotomy and a favorable age for postoperative rehabilitation. Moreover, delaying the hip osteotomy is also not recommended. Field et al[11] reported that 7 of their 11 patients who reached adolescence lost their ability to walk unaided and had generalized muscle weakness. They attributed this to the progressive joint contractures of the lower limbs, progressive subluxation and dislocation of hip joints, and increasing genu valgum developed in their patient population by the age of 10.

TABLE 5. Comparison of Radiographic Findings Between Nonsurgery Group and Surgery Group (Preoperative Radiographs)

	Nonsurgery Group	Surgery Group (Preoperative)	P
No. hips	62	40	—
Age (y)	5.7 (± 4.1)	6.8 (± 3.1)	0.17
AI-WBZ	31.9 (± 7.6)	33.3 (± 7.9)	0.38
LCEA	−1.7 (± 12.5)	−5.3 (± 10.9)	0.14
Migration (%)	51.2 (± 15.3)	50.7 (± 15.7)	0.83
FNSA	149.3 (± 7.5)	150.9 (± 5.8)	0.25

*P-value <0.05 is considered as statistically significant.

AI-WBZ indicates acetabular index of weight bearing zone; LCEA, lateral center edge angle; FNSA, femoral-neck-shaft angle.

TABLE 6. Comparison of Radiographic Findings Between Nonsurgery Group and Surgery Group (Recent Follow-up Radiographs) at Comparative Age Range

	Nonsurgery Group	Surgery Group (Recent Follow-up)	*P*
No. hips	28	40	—
Age range (y)	5.6-19.9	5.4-21.2	—
AI-WBZ	30.2 (± 6.2)	24.7 (± 8)	0.004*
LCEA	−0.6 (± 14.5)	9.6 (± 13.6)	0.006*
Migration (%)	50.8 (± 15.3)	35.2 (± 17.8)	< 0.001*
FNSA	149.4 (± 9.1)	130.8 (± 12.4)	< 0.001*

**P*-value < 0.05 is considered as statistically significant.
AI-WBZ indicates acetabular index of weight bearing zone; LCEA, lateral center edge angle; FNSA, femoral-neck-shaft angle.

Many patients with HS present a major anesthetic risk because of their upper airway obstruction, limited jaw motion, short neck, difficulty with intubation, and atlanto-axial instability. The risk of anesthesia has been reported to increase with age.[4] Several of our patients stayed in PICU for a night after surgery for close postoperative monitoring of their airway as well as hemodynamic check. No nonorthopaedic problems were encountered in this cohort of patients. All our patients underwent bilateral hip surgeries performed at the same time by 2 teams of orthopaedic surgeons working on either side. This reduces the duration of anesthesia and number of visits to the operating room. Doing 2 sides simultaneously also shortens postoperative rehabilitation time. However, bilateral hip surgery that includes bilateral femoral osteotomies and bilateral pelvic osteotomies in this patient population is a significant undertaking both in terms of the surgery as well as the rehabilitation afterwards. Many of the patients in the nonsurgical group in our study are awaiting surgery. Orthopaedic surgery for their hips and/or other lower extremity issues may be delayed or postponed for a number of reasons including: atlanto-axial instability, sometimes thoracolumbar kyphosis requiring stabilization first, other medical issues related to HS, and parental or surgeon preference.

Various studies reported that marked improvements noted in other clinical symptoms after HCT are not observed in the skeletal system.[2,4,5,9–12] Field et al[11] described 3 different patterns of skeletal growth disturbance in patients with HS. IDUA deficiency is thought to disturb "systemic bone modeling" by affecting primary ossification centers due to collection of GAG in these tissues, which is evident by their abnormal facial features (membranous bones) and short stature (endochondral ossification). A second theory is "focal failure of ossification," primarily noted at 3 sites: anterosuperior quarters of vertebral bodies of thoracolumbar junction (resulting in focal kyphosis),

TABLE 7. Comparison of Radiographic Measurements Between; Those With Age Under 5 Years at the Time of Surgery and Those Over 5 Years at the Time of Surgery (Combined P-FVDO and PO)

	Surgery at Age Under 5 y	Surgery at Age Over 5 y	*P*
No. hips	10	20	—
Age at HCT	1.4 (± 0.7)	1.8 (± 1.5)	0.40
Age at surgery	4.1 (± 0.4)	8.2 (± 3.0)	< 0.01
Time from HCT	2.7 (± 1.0)	6.3 (± 2.8)	< 0.01
BMI	18 (± 1.6)	18.4 (± 2.2)	0.663
Preoperative			
AI-WBZ	32.2 (± 7.8)	34.2 (± 9.2)	0.56
LCEA	−9.2 (± 11.7)	−4.2 (± 11.5)	0.28
Migration (%)	59.4 (± 15.3)	46.8 (± 16.3)	0.05
FNSA	154 (± 6)	149.9 (± 4.4)	0.05
Immediate postoperation			
AI-WBZ	21.4 (± 6.9)	23.2 (± 7.4)	0.53
LCEA	14.6 (± 10.7)	14.6 (± 16.7)	0.84
Migration (%)	29.1 (± 23.3)	27.2 (± 25.4)	1.00
FNSA	137 (± 8.9)	126.9 (± 11.3)	0.02
Recent follow-up			
Age at recent x-ray	11.0 (± 4.3)	14.2 (± 5)	0.11
Time from surgery (mo)	82.4 (± 53)	72.2 (± 45.1)	0.60
AI-WBZ	23.3 (± 7.6)	23.8 (± 7.3)	0.85
LCEA	8 (± 15.4)	14.4 (± 11.8)	0.25
Migration (%)	37.4 (± 17.4)	30.7 (± 16.4)	0.34
FNSA	139.5 (± 7.4)	123.8 (± 13.0)	0.002

**P*-value < 0.05 is considered as statistically significant.
AI-WBZ indicates acetabular index of weight bearing zone; BMI, body mass index; HCT, hematopoietic cell transplant; LCEA, lateral center edge angle; FNSA, femoral-neck-shaft angle; NS, not significant; P-FVDO, proximal femoral varus derotation osteotomy; PO, pelvic osteotomy.

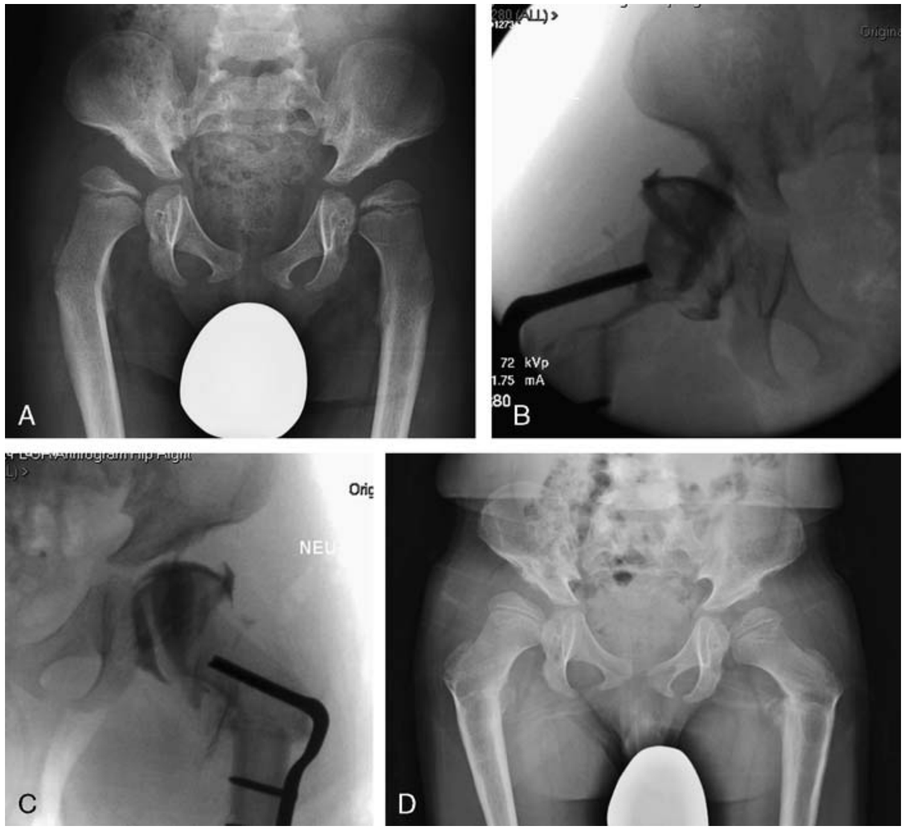

FIGURE 2. A, Anteroposterior (AP) pelvis radiograph of a boy (4 y 7 mo) demonstrating bilateral severe acetabular dysplasia, proximal femoral valgus deformity, and thin medial capital epiphysis, typical findings in patients with Hurler syndrome. B, Right hip arthrogram of same patient (A) after proximal femoral varus osteotomy showing different lateral margins of bony and cartilaginous acetabulum. C, Left hip arthrogram of same patient (A) after proximal femoral varus osteotomy showing different lateral margins of bony and cartilaginous acetabulum. D, Three-year postoperation AP pelvis radiograph of same patient (A) after bilateral proximal femoral plate removal, showing remodeling of proximal femur with increased height of medial capital femoral epiphysis.

lateral roof of the acetabulum (acetabular dysplasia), and lateral margin of the proximal tibial metaphysis (genu valgum).[11] Cartilaginous forms of tissue at these areas almost always fail to ossify normally in patients with HS. The hypothesis behind the failure of ossification is ineffective delivery of IDUA at these locations due to a combination of relatively poor blood supply and abnormal chondrocyte orientation within the growth plates. This theory explains the difference in results of isolated P-FVDO and P-FVDO + PO in our study.

We routinely perform intraoperative arthrogram in patients with HS after their femoral osteotomy to delineate the cartilaginous acetabular margin. We have found an arthrogram as a convenient, easy, and dynamic test that is helpful in the operating room to guide our decision-making. Moreover, arthrogram performed after femoral osteotomy and before pelvic procedure is true representation of the joint congruency, femoral head coverage, and cartilaginous margin, the information, which cannot be adequately obtained from a static preoperative magnetic resonance imaging (MRI). Therefore, in general we do not perform an MRI of the hips in patients with HS, which in itself is an invasive procedure for children at this age. Hip arthrograms performed during surgery in our patients most often showed a well-developed cartilaginous acetabular roof (Figs. 2B, C). This brings the possibility of improvement in bony acetabular coverage over time with the ossification of the lateral margin of the acetabulum. However, follow-up radiographs after isolated P-FVDO showed persistence of unossified lateral margin of the acetabulum with no improvement in AI and LCEA over time (Table 2). Field et al[11] also had similar observations with isolated femur osteotomies. There were no changes in the acetabulum in their patients who underwent isolated femoral osteotomies in the hope that the acetabulum will remodel. They attributed this to the failure of ossification of the lateral acetabular margin, and they concluded that doing only a femoral osteotomy was ineffective. Masterson et al[12] also concluded from their study on 8 patients that isolated femoral osteotomy does not seem to be sufficient in HS and PO serves as an essential part of the surgery. Our current study, with a large patient population, also has similar findings.

FIGURE 3. Anteroposterior pelvis radiograph of 14-year-old girl with Hurler syndrome status 9 years after bilateral proximal femoral varus derotation osteotomy + pelvic osteotomy.

All 40 hips in surgical group needed P-FVDO in the current study. Although, all preoperative x-rays were performed with the lower extremities in internal rotation, which presumably shows true valgus deformity, we do additionally verify the true valgus femoral-neck deformity versus rotational deformity by inserting a guide wire in the femoral-neck and examining femur under C-arm. After verification under fluoroscopy, a combined varus derotation osteotomy was performed in all our cases.

There were 3 different types of pelvic osteotomies performed in our study population, attributed to surgeons' experience, training, and preference depending on intraoperative arthrogram findings in a particular case. There was no difference in the results depending on the type of PO performed. However, it should be noted that the results of all of these studies including our own are based on radiographic results. As we neither have functional outcomes data nor long-term follow-up into adulthood for HS patients, we are unable to comment on whether improved radiographic correction of acetabular dysplasia and coverage correlates with better long-term hip function or a lower incidence of degenerative hip disease in patients with HS.

Field's third theory was termed "avascular disorder of the femoral head" and he called this event similar to Perthes disease.[11] Our observation about the shape of capital femoral epiphysis was similar to that of Field and colleagues. The medial part of the capital epiphysis was usually thin in these patients (Fig. 2A). However, we may not agree with Field in the comparison of the femoral head of patients with HS to those with Perthes disease because of the difference in pathoanatomy of the 2 conditions. First, in HS the medial side of the femoral head shows thinning which is unlike Perthes disease. Second, our observation in HS shows that medial epiphysial height improves after reconstructive osteotomies and shows no sequential stages as seen in patients with Perthes disease (Figs. 2A, B). We hypothesize that thinning of the medial side of the femoral capital epiphysis in HS is due to mechanical overloading of this region from the combination of proximal femoral valgus deformity and lateral migration of the head that brings the medial portion of the epiphysis under the weight bearing section of the hip. In addition none of our patients showed coxa magna like Perthes diseases.

Current practice guidelines in the pediatric literature suggest that minimum follow-up for patients with HS should be every other year for their musculoskeletal assessment, which can vary depending on particular patient requirement.[4,16] However, considering the severe form of hip dysplasia that is seen in patients with HS even after HCT, as well as, requirement of reconstructive hip surgery at young age, we recommend yearly orthopaedic evaluations. In addition, these patients should be monitored for other progressive skeletal abnormalities such as localized thoracolumbar kyphosis and genu valgum.

There are certain recognized limitations to this study, including its retrospective nature, the fact that surgeries were performed by more than 1 orthopaedic surgeon, and that no functional hip data are available. In addition, no histological or MRI findings are available to show the fate of the cartilaginous lateral margin of the acetabulum with growing age. Despite these limitations, it is the first report specifically focused on hip dysplasia in the largest cohort of patients with HS (102 hips) after HCT. In addition, this study represents the longest postoperative follow-up reported, comparing surgical and nonsurgical groups as well as differences between P-FVDO and combined P-FVDO + PO as a treatment modality (Fig. 3).

In conclusion, hip dysplasia in patients with HS is a significant orthopaedic problem even after recent advances in the treatment of these patients with HCT. As life expectancy of patients with HS is increasing with HCT, we recommend regular annual follow-up of their hips and reconstruction of their hip dysplasia with proximal femoral varus derotation and pelvic osteotomies.

REFERENCES

1. Meikle PJ, Hopwood JJ, Clague AE, et al. Prevalence of lysosomal storage disorders. *JAMA*. 1999;281:249–254.
2. Peters C, Steward CG, National Marrow Donor Program, International Bone Marrow Transplant Registry, Working Party on Inborn Errors, European Bone Marrow Transplant Group. Hematopoietic cell transplantation for inherited metabolic diseases: an overview of outcomes and practice guidelines. *Bone Marrow Transplant*. 2003;31:229–239.
3. Moore D, Connock MJ, Wraith E, et al. The prevalence of and survival in mucopolysaccharidosis I: Hurler, Hurler-Scheie and Scheie syndromes in the UK. *Orphanet J Rare Dis*. 2008;3:24.
4. Muenzer J, Wraith JE, Clarke LA, International Consensus Panel on Management and Treatment of Mucopolysaccharidosis I. Mucopolysaccharidosis I: management and treatment guidelines. *Pediatrics*. 2009;123:19–29.
5. Hobbs JR, Hugh-Jones K, Barrett AJ, et al. Reversal of clinical features of Hurler's disease and biochemical improvement after treatment by bone-marrow transplantation. *Lancet*. 1981;2:709–712.
6. Whitley CB, Belani KG, Chang PN, et al. Long-term outcome of Hurler syndrome following bone marrow transplantation. *Am J Med Genet*. 1993;46:209–218.

7. Braunlin EA, Hunter DW, Krivit W, et al. Evaluation of coronary artery disease in the Hurler syndrome by angiography. *Am J Cardiol*. 1992;69:1487–1489.
8. Guffon N, Souillet G, Maire I, et al. Follow-up of nine patients with Hurler syndrome after bone marrow transplantation. *J Pediatr*. 1998;133:119–125.
9. Silveri CP, Kaplan FS, Fallon MD, et al. Hurler syndrome with special reference to histologic abnormalities of the growth plate. *Clin Orthop Relat Res*. 1991;269:305–311.
10. Weisstein JS, Delgado E, Steinbach LS, et al. Musculoskeletal manifestations of Hurler syndrome: long-term follow-up after bone marrow transplantation. *J Pediatr Orthop*. 2004;24:97–101.
11. Field RE, Buchanan JA, Copplemans MG, et al. Bone-marrow transplantation in Hurler's syndrome. Effect on skeletal development. *J Bone Joint Surg Br*. 1994;76:975–981.
12. Masterson EL, Murphy PG, O'Meara A, et al. Hip dysplasia in Hurler's syndrome: orthopaedic management after bone marrow transplantation. *J Pediatr Orthop*. 1996;16:731–733.
13. Taylor C, Brady P, O'Meara A, et al. Mobility in Hurler syndrome. *J Pediatr Orthop*. 2008;28:163–168.
14. Massie WK, Howorth MB. Congenital dislocation of the hip. Part I. Method of grading results. *J Bone Joint Surg Am*. 1950; 32-A:519–531.
15. Reimers J, Poulsen S. Adductor transfer versus tenotomy for stability of the hip in spastic cerebral palsy. *J Pediatr Orthop*. 1984;4:52–54.
16. Pastores GM, Arn P, Beck M, et al. The MPS I registry: design, methodology, and early findings of a global disease registry for monitoring patients with mucopolysaccharidosis type I. *Mol Genet Metab*. 2007;91:37–47.

