

Orthopedic management of mucopolysaccharide disease

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Abstract. With advances in the treatment of the mucopolysaccharidosis (MPS) disorders, musculoskeletal problems are increasingly becoming a focus of care for these patients. This review discusses the current understanding of the pathophysiology of musculoskeletal disease in MPS and its orthopedic management. Deformities of the spine, hips and extremities are common and often functionally limiting. Carpal tunnel syndrome and flexor tendon triggering are common. Surgical intervention is often required to optimize long-term function.

Keywords: Mucopolysaccharidosis, orthopedics, spine, hip, knee

1. Introduction

The mucopolysaccharidoses (MPS) constitute a family of lysosomal storage diseases resulting from an inborn error of metabolism and subsequent abnormal accumulation of cellular glycosaminoglycans (Table 1). Mucopolysaccharides, or glycosaminoglycans (GAGs), are important constituents of the connective tissue matrix, and play a critical role in collagen-matrix adhesion, and consequently cell and tissue integrity. Abnormal accumulation of these molecules disrupts most normal organ system processes [9,22,25,29,32]. Depending on the degree of enzymatic defect, the MPS disorders can be characterized by a large spectrum of clinical involvement. Multiple organ system involvement is typical and includes central nervous system, cardiopulmonary solid organ, ocular and musculoskeletal disease. The skeletal disease manifestations range from mild platyspondyly with or without epiphyseal dysplasia to severe, life-threatening spinal deformities

and crippling hip deformities [9,19,47]. Both joint stiffness and ligamentous laxity are associated with MPS disorders, compounding the problems associated with the skeletal deformities.

Dysostosis multiplex, the constellation of radiographic abnormalities classically seen in MPS, results from defective endochondral and membranous growth throughout the body, including the hips, knees and spine [5,8,31]. Additional findings include enlargement of the skull, a thick calvarium, J-shaped sella turcica, broad clavicles and ribs. The molecular physiology of this problem is not yet completely understood. Dysregulation of many structurally related cytokines has been described in MPS animal models, including MMP-13, FGF-2 and elastin binding protein [10,27,35]. Examination of the physes from MPS I animal models and human biopsy specimens reveals growth plates that are wider than normal, with the widening being dispersed over all anatomic zones [5,31,34]. The quality of cells appears grossly normal in the reserve and proliferative zones, but electron microscopy reveals enlarged, vacuolated cytoplasm. The zone of hypertrophy is hypercellular and demonstrates increasing disorganization. The zone of provisional calcification

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Table 1
Orthopedic findings in the Mucopolysaccharidoses

	Eponym	Enzyme Deficiency	Cervical Stenosis	Occipital-Cervical Instability	Thoracolumbar Kyphosis	Scoliosis	Hip Dysplasia	Proximal Femoral Epiphyseal Dysplasia	Genu Valgum	Carpal Tunnel Syndrome
MPS I (severe)*	Hurler	α -L-Iduronidase	2+	1+	3+	2+	3+	1+	2+	2+
MPS I (attenuated)	Hurler-Scheie, Scheie	α -L-Iduronidase	2+	0	0	0	0	0	0	3+
MPS II	Hunter	Iduronate sulfatase	1+	0	1+	1+	1+	1+	0	2+
MPS III	Sanfilippo	Heparan N-sulfatase, α -N-Acetylglucosaminidase, Acetyl CoA: α -glycosaminide acetyltransferase, N-Acetylglucosamine 6-sulfatase	0	0	0	1+	0	2+	1+	0
MPS IV	Morquio	Galactose 6-sulfatase, β -Galactosidase	2+	3+	2+	0	1+	3+	3+	0
MPS VI	Maroteaux-Lamy	N-Acetylgalactosamine 4-sulfatase (arylsulfatase B)	3+	3+	1+	0	2+	2+	0	1+
MPS VII	Sly	β -Glucuronidase	?	?	?	?	?	?	?	?

*post. HSCT

0 = not reported

1+ = rare

2+ = common

3+ = frequent

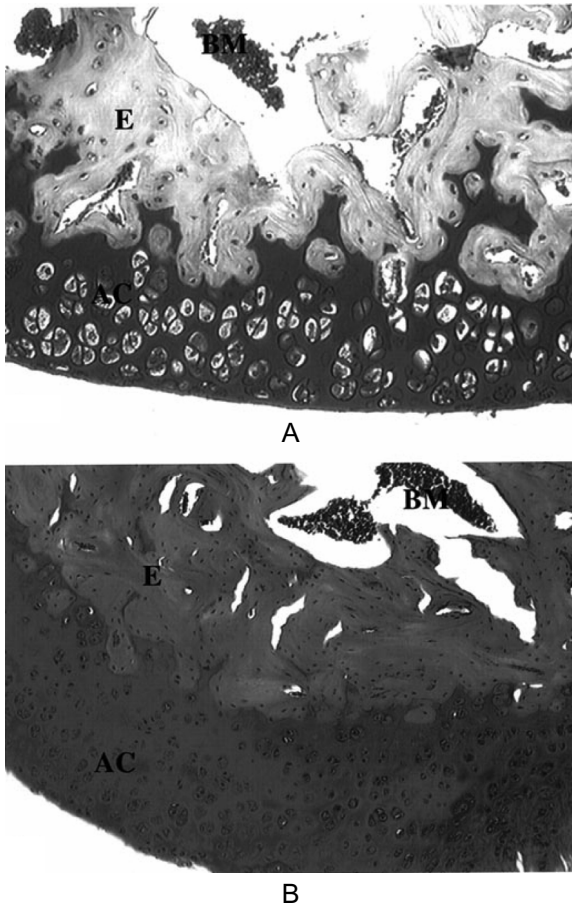


Fig. 1. Proteoglycan depletion in the articular cartilage of MPS VI rats. Longitudinal sections of 6-month-old MPS VI (A) and normal (B) rat proximal tibia were stained with safranin-O to visualize proteoglycans. BM, bone marrow; E, epiphyses; AC, articular cartilage. Note that the epiphyses of the MPS VI rats stained less intensely than those of normal rats of the same age. Magnification, x 40. (Figure taken from Simonaro et al., *Lab Invest* **81**(9) (2001), 1319–1328).

is also enlarged and disorganized. Incomplete breakdown of the physal cartilage matrix, leads to disorganized ossification with islands of remnant cartilage and erratic cortical bone formation in the primary spongiosa. These processes become more pronounced with maturity and ultimately result in the observed skeletal dysplasia [31].

Articular cartilage is also abnormal in MPS disorders. This has been demonstrated by arthroscopy in patients with MPS IV and in animal models with MPS VI [15,37]. Histopathology and biochemical analysis demonstrate proteoglycan and collagen depletion in articular cartilage matrix. This is thought to be the result of dermatan sulfate induced nitric oxide (NO) and tumor necrosis alpha (TNF- α) release, and subsequent

chondrocyte apoptosis [37]. These findings likely result in the subchondral delamination that has been observed arthroscopically (Fig. 1).

Because musculoskeletal deformities account for greater than 40% of the presenting signs for some MPS disorders [45], familiarity with these disorders is critical, not only for recognition and diagnosis, but for treatment of these devastating diseases. Early diagnosis allows time-sensitive medical treatment, particularly in those disorders responsive to hematopoietic stem cell transplantation (MPS IH and MPS VI) [4,17,28,33]. Hematopoietic stem cell transplant (HSCT), while often life-saving through the alleviation of disease for the majority of major organ systems, does not alter the course of progressive skeletal disease, although some normalization of articular cartilage and linear growth may occur [5]. Enzyme replacement therapy (ERT) on the other hand, has been shown to reduce the burden of skeletal disease in MPS VI cats treated from birth [2].

Regardless of the method of specific treatment, it has become increasingly clear that children with even the most severe forms of MPS are now living into adolescence, and conceivably beyond. If left untreated, these skeletal problems usually become functionally limiting and often painful [8]. The goals of surgical procedures for the spine, hips, knees and hands should be to promote optimal function and gait. Surgical and non-surgical management of the musculoskeletal manifestations of MPS are discussed here.

2. Cervical spine

Issues involving the cervical spine are extremely common in children with MPS, and may be potentially life-threatening. Atlantoaxial instability with resultant myelopathy and spastic quadriplegia is well described in MPS IV and MPS VI [12,19,40,43] (Fig. 2a, b). Quadriplegia is a known cause of premature death in affected individuals [19]. In addition, GAG accumulation behind the odontoid process may result in progressive stenosis and resultant compression of the spinal cord at the occipital-cervical junction [38]. Consequently, prophylactic fusion, often with decompression, has been recommended in all individuals affected by MPS IV [19,30]. In MPS I, growth of the odontoid process may normalize after HSCT, but enlargement of the odontoid process continues [11,13,47]. Thus, spinal instability and spinal cord compression may still occur, but may be less common.

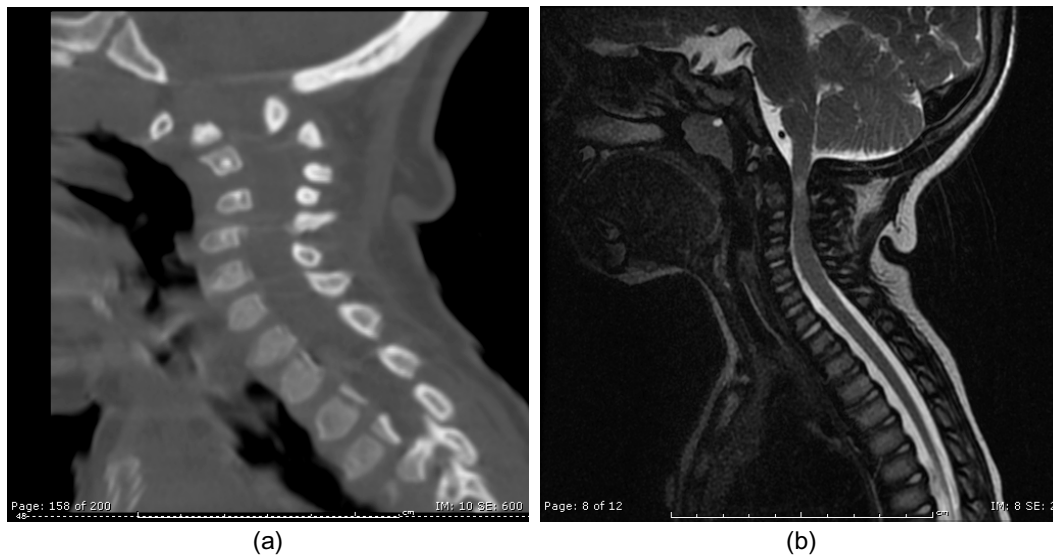


Fig. 2. CT scan (a) and MRI (b) from a two year-old child with MPS VI seen 6 months after a fall backwards from standing. The patient was partially quadriparetic, but had recovered most function at the time of evaluation. He subsequently underwent C1 decompression and occipital-cervical fusion. Images show anterior displacement of C1 on C2 with resultant stenosis on CT scan. Myelomalacia is appreciated at the same level with the posterior arch of C1 impinging on the spinal cord.

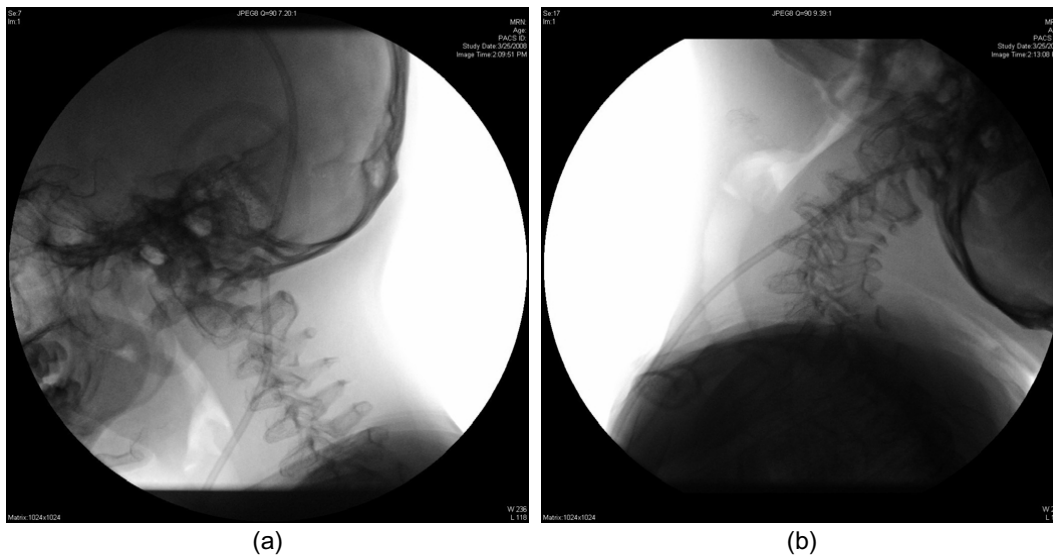


Fig. 3. Dynamic fluoroscopic images taken of the cervical spine in this eight year old MPS I patient, while awake, demonstrate subtle motion between the occiput and C1, and posterior widening between C1 and C2. This patient had received a matched cord blood transplant.

Atlanto-axial instability is often not demonstrated on flexion-extension cervical spine films [48]. It is unclear whether this lack of hypermobility is a failure of adequate imaging due to patient splinting. Dynamic fluoroscopy on an awake patient can unmask instability not seen on static flexion-extension plain films [49] (Fig. 3). The pathophysiology of cervical stenosis in MPS may result from delayed ossification of the odontoid pro-

cess. The persistent cartilaginous anlage is prone to repetitive trauma, and at times, fracture [30,38]. This odontoid trauma results in two distinct problems that contribute to spinal cord injury. The first is atlanto-axial instability, which results from dens fracture and associated ligamentous instability. This is commonly demonstrated on flexion-extension radiographs. The second is cartilage/fibrocartilage reactive hypertrophy around

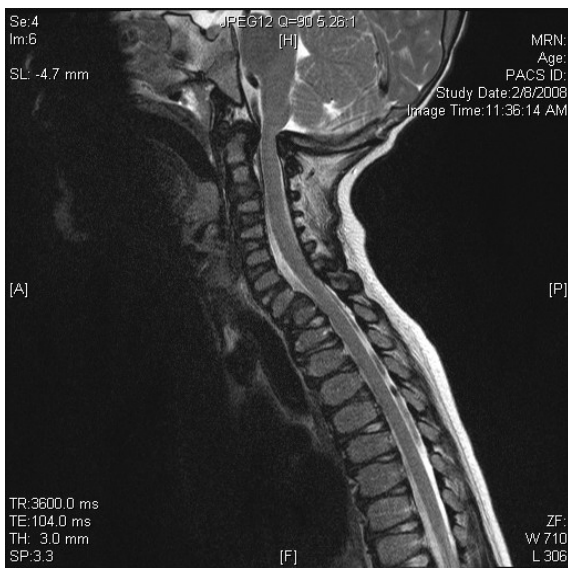


Fig. 4. An MRI from the same MPS I patient (from Fig. 4) shows significant stenosis between a retroverted odontoid process with overlying hypertrophic cartilage and the foramen magnum.

the odontoid process, as demonstrated on pathology samples by Ashraf et al. [1,24], compounded by thickening of the dura and ligamentum flavum hypertrophy, both of which have been demonstrated by imaging and pathology specimens [13,24]. This process results in cervical stenosis and cord compression from a combination of odontoid fibrocartilage hypertrophy, ligamentous laxity and soft tissue thickening [1,38].

Atlantoaxial instability has been reported in MPS VI (Maroteaux-Lamy) and in severe, untreated MPS I (Hurler) [6,42,43]. Children with MPS I, who have undergone hematopoietic stem cell transplant (HSCT) often have normalization of their odontoid process [11]. Many of these patients however continue to demonstrate deposition of GAGs in the subarachnoid space directly behind the C2 vertebra [11,13], and some have required surgical treatment of cervical spine disease after HSCT (Fig. 4). Even the more attenuated forms of MPS I (Hurler-Scheie and Scheie) develop surgical-grade cervical stenosis with myelopathy in the upper cervical spine and require careful monitoring for this process [45].

Multilevel cervical stenosis has also been reported in MPS VI (Maroteaux-Lamy), in addition to atlantoaxial instability [1]. Imaging in these patients reveals posteriorly prominent intervertebral discs, thickened dura and hypertrophy of the ligamentum flavum. This finding is also demonstrated in the MPS VI cat model (Mark Haskins, personal communication). Pathology

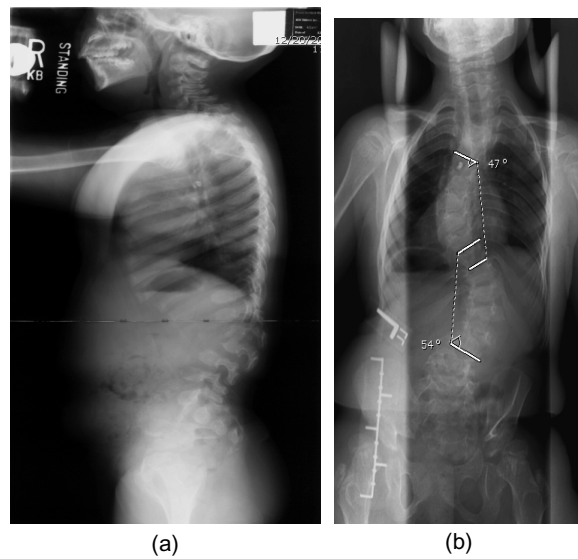


Fig. 5. A typical thoracolumbar kyphosis (a) is seen in this nine year old girl with MPS I after matched unrelated bone marrow transplantation. She also developed a significant double major scoliosis. She continues to be observed without any interventions.

samples taken at the time of durotomy show the classic MPS cellular pathology with cells filled with enlarged lysosomes due to GAG accumulation [13]. In the absence of instability, cervical decompression without fusion may be appropriate.

Several authors have recommended prophylactic decompression and fusion of the occipital cervical junction at an early age for MPS IV [19,30,38]. Current recommendations are for decompression and fusion of asymptomatic patients when the space available for the cord is < 14 mm or there is cervical instability > 8 mm. Patients with 5 to 8 mm of cervical instability, with clinical evidence of spinal cord impingement, and all patients with a deteriorating neurological condition also warrant surgical treatment [48].

It is recommended that all children with MPS should avoid “high risk” activities such as contact sports, gymnastics, etc. In addition, these children should be treated with caution when undergoing positioning for anesthesia, and at least one set of flexion and extension lateral radiographs of the cervical spine is recommended prior to anesthesia in all affected individuals to evaluate for atlantoaxial instability.

3. Thoracolumbar spine

The hallmark orthopedic feature in MPS is thoracolumbar kyphosis or the gibbus deformity, and has

historically played a significant role in the diagnosis of MPS [3,45]. Gibbus deformities occur in nearly all children with severe MPS I, and are commonly found in other MPS disorders [8] (Fig. 5a). The kyphosis develops from poor bone growth in the anterior-superior aspect of the upper lumbar vertebrae. This process results in anterior wedging, retrolisthesis of the apex vertebrae and anterior herniation of the intervertebral discs at the thoracolumbar junction [18]. Surgical stabilization to halt the progression of the kyphosis is relatively common in MPS I and in MPS VI, even after HSCT [8, 9,47]. Scoliosis has been observed in MPS I, II, III, but is rarely significant enough to require surgery [9] (Fig. 5b).

There is no clinical evidence to support the use of bracing in MPS. Bracing may slow the progression of both spinal kyphosis and scoliosis, delaying surgery, but not preventing surgery. Bracing can be uncomfortable for children, and they rarely tolerate it, especially young children due to their stature and abdominal girth. Consequently, bracing is only recommended in young children with progressive deformity who are not otherwise candidates for surgery. One must consider the psychosocial implications for the patients and their families.

Indications for surgery vary, depending on the needs of the child and the desires of the family. Generally, a kyphosis of more than 70° or scoliosis greater than 50° are relative indications for surgery. (James Ogilvie, personal communication) The presence of myelopathy is clearly an indication for surgery. Often the medical complexity of these patients can be a factor against surgical intervention. Surgery for kyphosis or scoliosis may be necessary as young as two years of age, and usually before adolescence. Published reports put the average age at about eight years [8]. Current experience suggests that, if possible, delaying spinal surgery allows maximal growth of the spine and further development of already osteopenic and small, dysplastic bone, thus reducing the technical difficulty of the procedure.

Anterior and posterior fusion for kyphotic deformities is recommended, followed by postoperative bracing for 3–6 months. Early experience suggests that treatment of kyphosis by posterior instrumentation and fusion only may lead to an increased risk of failure and the need for re-operation. (James Ogilvie, personal communication) In general, when these guidelines are followed, there does not seem to be an increased risk of pseudoarthrosis (failure for bones to fuse) in this patient population. Treatment of scoliosis follows traditional indications for intervention in complex deformity,



(a)



(b)

Fig. 6. An anteroposterior view of the hips (a) in a patient with MPS I, after matched unrelated bone marrow transplantation, demonstrates significant hip dysplasia with a poorly developed acetabulum, coxa valga, and apparent subluxation of the femoral heads. An arthrogram taken three years previously demonstrates a well developed cartilaginous anlage which failed to ossify.

including the recommendation for anterior fusion in less mature children in order to prevent crankshaft phenomenon.

4. Hips/pelvis

Hip concerns are present in nearly all individuals with MPS, and can be divided into two major categories: hip dysplasia and osteonecrosis-like epiphyseal dysplasia [8,16,20,41,47]. In MPS-related hip dysplasia there is a poorly developed acetabulum, underdevelopment of the medial portion of the proximal femoral epiphysis, and coxa valga. There appears to be delayed ossification of the lateral acetabular corner, leaving a significant cartilaginous anlage as demonstrated by arthrogram (Fig. 6a, b). In our experience, MRI images confirm these arthrography findings. This com-

combination of bone defects results in progressive hip instability and late dislocation. This can be functionally limiting by adolescence or early adulthood [8].

Epiphyseal dysplasia, which has the appearance of osteonecrosis, or Perthes Disease, is seen in MPS III, IV and VI (Fig. 7a). This process may represent an inflammatory mediated apoptosis [36]. Surgical reconstruction will not correct these deformities; however the role of containment surgery has not been investigated, and may be appropriate in selected cases. Ultimately, prosthetic replacement of the hip may be required (Fig. 7b). This is an extremely challenging procedure in patients with MPS, and should be reserved for individuals with incapacitating hip pain, and performed by surgeons versed in complex hip reconstructive surgery. In the future, early medical treatment with intra-articular anti-inflammatory medications may reduce the theoretical apoptosis and subsequent osteonecrosis-like processes [35].

Hip dysplasia to some degree is found in nearly all children with severe MPS I, and can also be found in children with attenuated MPS I, MPS II, MPS VI, and less often MPS IV [16,41,49]. Abduction bracing in young children with MPS has not been studied, but is likely ineffective and may actually result in worsening muscle weakness and delay of physical development. Hip dysplasia has not been shown to respond to stem cell transplant or enzyme replacement therapy although very early treatment after birth has not been well studied, and most children with MPS I after HSCT eventually require corrective hip surgery. Surgery on the hips is performed more easily at a younger age, around age 5–7, for an optimal outcome, but has been reported in children as young as 2 years of age. Technically, successful surgery becomes much more difficult at older ages (after triradiate cartilage closure).

Surgical reconstruction for hip dysplasia (primarily in MPS I) is a combination of osteotomies intended to reposition the bones and optimize hip mechanics [16, 41]. A pelvic osteotomy such as described by Salter, or Dega (as modified by Mubarak et al.) is required to reduce the global acetabular deficiency [21,46]. A proximal femoral osteotomy is also required to reduce the significant valgus deformity of the femoral neck. On occasion, capsulorrhaphy is required when the hip is dislocated. It should be noted that the hip capsule can be extremely thick and difficult to work with (up to 10 mm thick, personal communications, James Oglvie) Without hip surgery, there may be progressive pain and stiffness, and eventually frank dislocation of the hips, with a dramatic reduction in walking ability [8]. Thus far, the results of hip surgery in MPS are promising, resulting in improved motion and independent walking.



(a)



(b)

Fig. 7. Severe epiphyseal dysplasia with erosion and collapse of the femoral heads and subsequent subluxation in a twenty-four year old woman with MPS IV. She sustained a right femoral neck fracture which was stabilized with a screw (a). Due to severe pain symptoms, she underwent left total hip arthroplasty (b).

5. Knees

Almost all children with MPS IV, and about 50% of children with MPS I post-HSCT, develop genu valgum severe enough to require surgery [7,22,26]. Children with MPS VI as well as the attenuated forms of MPS I, can also develop knock-knees severe enough to warrant surgery. The published indication for surgery is a tibial-femoral angle greater than 15° . Hemiepiphyseal growth modulation through the use of Blount's staples may be performed through a relatively small incision [7, 26] (Fig. 8). A newer technology, the tension band plate ("8-plate", Orthofix, Verona, Italy), is showing great promise as an alternative to staples, particularly in children too small for staple placement [39]. Occasionally, these implants can dislodge. When this happens, they are typically removed, and if necessary, new ones

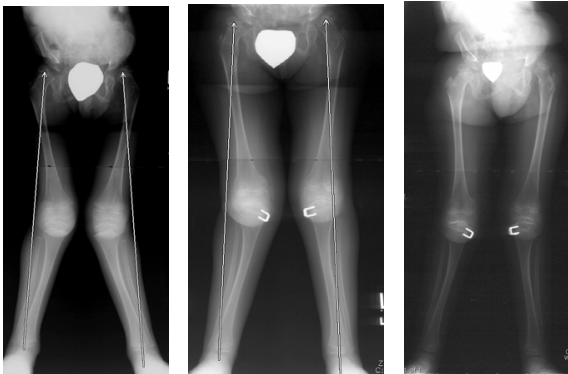


Fig. 8. The patient from Figure 6 also had significant genu valgum and had Blount's staples placed for growth modulation. In the time period covered, she showed progressive improvement of her deformity as demonstrated by the decrease in medial deviation from the mechanical axis (shown as white arrows). Surgical intervention has been recommended when the tibiofemoral angle exceeds 15° (also shown in first figure to the left - α).

replace them. Osteotomies near the knee (tibia or femur) may be required. Although osteotomies are more invasive and painful, staples or tension band plates will not work in children who are physically too small to have them placed, or those who do not have enough growth remaining to modulate. Growth in MPS can be difficult to predict, and as such criteria for intervention can not necessarily follow those of normal children. Experience with hip surgery has shown that children with MPS heal osteotomies well. Advanced arthrosis of the knee due to delamination of articular cartilage, in adults with MPS, may be addressed with total knee arthroplasty [7].

Children with MPS also suffer from stiff knees, which prevent full straightening and result in a crouched gait. Knee stiffness is improved with stem cell transplant and enzyme replacement therapy, but most children still require continued physical therapy to optimize knee motion and walking function [14,23]. For those with fixed knee flexion contractures, extension osteotomy of the distal femur should be considered.

6. Upper extremities

Upper extremity function may be adversely altered due to restricted joint motion, bony abnormalities, compression neuropathies or tenosynovial thickening. ERT has proven to be extremely beneficial in improving joint range of motion of the shoulders and elbows [14, 23]. The full benefits of ERT in this regard may take

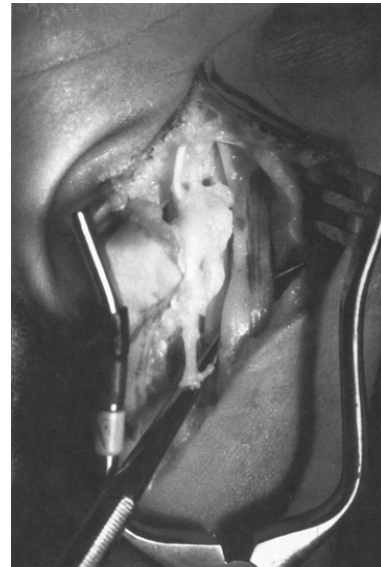


Fig. 9. Intraoperative view of a carpal tunnel decompression in a child with MPS I. Note the hourglass appearance of the median nerve adjacent to the large soft tissue accumulation sitting in the left half of the incision.

several years, however, to manifest themselves. Forearm pronation and supination are often limited by a Madelung's type deformity (most often seen in MPS II) [49]. Carpal tunnel syndrome, either due to primary neuropathy or secondarily from tenosynovial accumulation of GAGs, is well described in MPS disorders [44,50]. Median nerve neuropathy frequently goes unrecognized in children with limited expressive skills resulting in permanent loss of nerve function. As such, regular electrodiagnostic studies (nerve conduction velocities performed every one to two years) are recommended in children with MPS. Carpal tunnel release is required when median nerve disease exists or is suspected. Tenosynovial accumulation of GAGs also is known to result in "trigger digits" [44]. Surgical release is recommended when this condition exists as well, and can be done concomitantly with carpal tunnel release (Fig. 9). Delayed treatment of trigger digits may result in fixed flexion contractures.

7. Summary

Even with stem cell transplant or enzyme replacement therapy, patients with MPS continue to have significant muscular and skeletal disabilities, most commonly involving the spine, hips, knees and hands. These are rarely catastrophic or life threatening, but

frequently limit a child's function, activity, and quality of life. Surgical intervention is often required, to optimize long-term function. The timing and type of surgery may vary among children and among surgeons. Regardless, early evaluation is critical in determining what treatments will be necessary to optimize the quality of life for a child with MPS.

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Conflicts of interest

Klane White has received honoraria for educational lectures from BioMarin Pharmaceutical Inc., and Shire plc. Paul Harnatz has provided consulting support and received speaker's honoraria and travel support from BioMarin.

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