Early Diagnosis of the Mucopolysaccharidoses (MPS): An Orthopedic Perspective

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Disclosures

1. I am an orthopedic surgeon
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Objectives

1. Identify early skeletal manifestations of MPS
2. Describe surgical decision making and treatment options for skeletal disease in MPS
3. Describe the role of medical therapies in MPS

The Mucopolysaccharidoses

• Single gene (enzyme) defect
• Inborn error of metabolism
• Lysosomal storage disorder
• Multiple organ disease
  – CNS
  – cardiopulmonary
  – solid organ
  – ocular
  – musculoskeletal
An Orthopedic Perspective
Dysostosis Multiplex

- Diffuse skeletal disease
- Specific to MPS
- GAG mediated inflammation
- Progressive deformity early in life (not reversible)
- Later joint degeneration (arthritis) and deformity

The Mucopolysaccharidoses

- Failed conversion of cartilage to bone
- Chondrocytes fail to transition from proliferative to hypertrophic phase
- Extracellular GAGs alter distribution and availability of growth factors
- Aberrant processing of Sox9???
Musculoskeletal Presentation in MPS

MPS 1H:
- Gibbus / thoracolumbar kyphosis (97.2%)
- Hip dysplasia (82.4%)
- Genu valgum (51.0%)

MPS 1H-S or MPS 1S:
- Joint stiffness (44%)
- Finger flexion deformity (8%)

(Aldenhoven et al, 2015, Vijay and Wraith 2005)
Importance of surgical history in diagnosing mucopolysaccharidosis type II (Hunter syndrome): Data from the Hunter Outcome Survey.

Mendelsohn, Nancy; Harmatz, Paul; Bodamer, Olaf; Burton, Barbara; Giugliani, Roberto; Jones, Simon; MB, Lampe, Christine; Malin, Gunilla; MD, PhD, Steiner, Robert; Parini, Rossella

Genetics in Medicine. 12(12):816-822, December 2010. DOI: 10.1097/GIM.0b013e3181f6e74d

Fig. 2. Age at first surgical procedure of patients in the Hunter Outcome Survey (HOS). Data are from patients in HOS for whom the date of the first of the specified type of operation was known (numbers of patients shown in parentheses).

Fig. 3. Proportion of patients in the Hunter Outcome Survey (HOS) in whom the first specified surgical intervention preceded diagnosis. Data are from patients for whom the date of diagnosis of MPS II and the date of the first of the specified type of operation were known (Table 3).
Musculoskeletal abnormalities are the most common presenting features in Morquio A

![Bar chart showing percentage of subjects with various musculoskeletal abnormalities: Pelvis camptalgia 97%, Abnormal gait 94%, Short stature 93%, Genital deformity 93%, Short neck 91%, Joint laxity 87%, Kyphoscoliosis 85%, Joint stiffness/pain 83%, Hip dysplasia 71%]

n = 325 subjects
Data based on medical history reviews


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Clinical characteristics of adults with slowly progressing mucopolysaccharidosis VI: a case series

Anke Thimler - Elke Mielbach - Christina Lampe - Susanne Pitz - Wolfgang Kamin - Christoph Kampmann - Bianca Link - Eugen Mengel

Changes with valve replacement in three, two underwent craniocervical decompression surgery, two underwent carpal tunnel surgery, five had ear/nose/throat (ENT) interventions, seven had hip pain/dysplasia, seven had corneal...
Early recognition of MPS: radiographic findings
Hurler (MPS IH)

- L1 hypoplasia (>90%)
- Acetabular dysplasia
- Broad ribs
- J-shaped sella turcica
- Normal hands
- Advanced bone age? (increased # of carpal bones)

4 mos old female
MPS IH
Hunter (MPS II)

- J shaped sella turcica
- Broad ribs
- Coxa valga
- “Madelung’s” deformity
- L1 hypoplasia
Morquio (MPS IV)

- Generalized vertebral hypoplasia  
  (with kyphosis)
- Acetabular dysplasia
- Hypoplastic, eccentric femoral epiphyses
- Short broad metacarpals with tapering
- “Madelung’s” deformity

3 year old female  
MPS IV
Maroteaux-Lamy (MPS VI)

- Vertebral hypoplasia
- Acetabular dysplasia
- Hypoplastic femoral epiphyses
- Coarsened diaphyses
- J-shaped sella turcica
Sly Syndrome (MPS VII)

- Skeletal differences known
- Not enough experience to identify early skeletal signs

MPS VII - 2 mos male

- 35 weeks gestation
- Birth weight 3.35 kg (94th%), length 48.3 cm (79th%), and OFC 33 cm (67th%)
- Apgar scores were 6 and 7
2 month old boy

- Dysmorphic facial features, thrombocytopenia and renal failure
- Respiratory distress requiring intubation hepatosplenomegaly
- Bilateral profound hearing loss and bilateral inguinal hernias
- Direct hyperbilirubinemia, mild transaminitis, thrombocytopenia

LABORATORY STUDIES:
- Beta-glucuronidase activity: 4 units (normal 165-585)
- Urine MPS: 115
- MPS/creatinine ratio: 1278
- Lysosomal enzyme screen: Low beta glucuronidase activity
• **Echocardiogram:** Large aneurysmal PDA. Mild branch pulmonary artery stenosis. Patent foramen ovale with left-to-right flow.

• **EKG:** Sinus tachycardia, biventricular hypertrophy, nonspecific T-wave abnormality.

• **Bone survey:** Mild anterior-inferior beaking of the L2 vertebral body and to a lesser degree, the L3 vertebral body. Mild thoracolumbar gibbus deformity.

**MPS VII - 2 mos male**
Radiographic Diagnosis (classical)

- Generalized vertebral hypoplasia
  
- Acetabular dysplasia

- Hypoplastic, eccentric femoral epiphyses

- Short broad metacarpals with tapering

- “Madelung’s” type deformity

Radiographic Red Flags: MPS

Vertebral body abnormality:

- Hypoplasia

- Beaking

- Kyphosis/Gibbus
Radiographic Red Flags: MPS

Bilateral hip osteonecrosis – Symmetric “Perthes”

Who To Refer To A Geneticist: Patients Diagnosed Radiographically With Any Of These Disorders Without Confirmatory Testing

- MED
- SED
- Bilateral Legg-Calvé-Perthes disease
- Pseudoachondroplasia
- Undiagnosed skeletal dysplasia

Refer to Genetics to rule out or confirm Morquio A with an enzyme activity analysis

Surgical Management in MPS

Spine Deformity in MPS

- Occipital-cervical
- Cervico-thoracic
- Thoraco-lumbar
- = Spinal cord compression

(Solanki et al. 2013)
Cervical Stenosis/Instability

From Hosalker et al. 2008

Cervical Spine Instability

From Hosalker et al. 2008
Surgery - Cervical Spine

Indications for fusion/decompression:

- Neurological Changes
- Clear instability
- MRI evidence of cord injury

(White et al, 2009)

Thoracolumbar Kyphosis (Gibbus)

- Most common spinal deformity in MPS
- Not always progressive

(Garrido et al. 2013)
Surgery - Kyphosis

- Anterior column
- Use interbody grafts or struts
- Posterior fusion (instrument if able)
- Brace for ≈ 3 mos

Scoliosis

- Much less common
- Pulmonary compromise
Surgery - Scoliosis

- Posterior fusion segmental fixation
- Anterior fusion in immature spines
- Growing Rods in younger Children?
Hip Dysplasia

- Femoral head erosion
- Progressive subluxation
- Painful arthrosis
Hip Deformity Correction

- Pelvic osteotomy + femoral osteotomy
  - Hip subluxation may recur
- Shelf acetabuloplasty + VDRO reported to yield good outcomes with no recurrent hip subluxation

San Diego osteotomy

Genu Valgum - Knock Knees

- Presents early (age 3-4 years)
- Affects mobility
- Generally responsive to “guided growth”
Hands

Carpal Tunnel Syndrome (CTS)

Trigger Fingers

MPS I, II, VI, VII


CTS in MPS

- Thickened tenosynovium and connective tissue from excessive GAG storage:
  - Presents with decreased function
  - **Painless**

(VanHeest et al, 1998)
Hands

Yearly nerve conduction studies - NCS
(No needles!)
Carpal tunnel/trigger releases
Occupational/Hand therapy

Medical Management
Hematopoietic Stem Cell Transplant (HSCT)

• First transplant for MPS (Hurler) in 1981
• Initially, transplantation possible for patients with matched sibling donor
• New sources of donors have become available (peripheral stem cells, cord blood)

Event-free survival MPS I (Hurler syndrome): Outcome by when transplant was done

(Boelens et al. 2013)
Stem Cell Transplant

Cognitive benefit in MPS I-H

Addresses somatic manifestations

Survival 65-89% at 3 years

Does not prevent orthopaedic deformities

(Souillet et al. 2003; Staba et al. 2004; Guffon et al. 2009; Field et al. 1994; Weisstein et al. 2006)
MPS IH Hip Dysplasia

Spinal Cord Compression - HSCT

(Aldenhoven et al., 2015)
CTS after HSCT

Enzyme Replacement Therapy

- ERT available since:
  - MPS I 2003
  - MPS VI 2005/2006
  - MPS II 2006/2007
  - MPS III IT Clinical trials
  - MPS IV 2014
  - MPS VII 2016
Enzyme Replacement Therapy

ERT in MPS

Accelerates rate of growth
Reduces joint stiffness
Decreases fatigue
Reduces spleen / liver
Improves pulmonary
Does not cross BBB
Summary

MPS disorders present with many musculoskeletal manifestations

Surgical treatment is a mainstay of care of orthopedic manifestations

Medical advancements are changing management continuously

Thank You!!

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