The Natural History of Cervical Spinal Cord Compression in Mucopolysaccharidosis

Evidence for asymmetric disease progression

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Conflict of Interest

- I have been involved in clinical trials for Biomarin and Shire
- I have received honoraria and travel grants from Biomarin
- I have provided consultation to advisory boards and attended expert’s meetings supported by Biomarin
MPS IVA patients present with marked musculoskeletal abnormalities

- Skeletal dysplasia
  - Spinal abnormalities
  - Pectus carinatum
  - Hip dysplasia
  - Genu valgum
  - Ankle valgus
  - Hand abnormalities
  - Flat facial features
  - Mandibular protrusion
- Short stature
- Joint instability
- Joint subluxation
- Joint degeneration
- Abnormal gait
- Weak hand grip

Left image: Kalteis et al, Arthroscopy, 2005
Musculoskeletal abnormalities are the most common presenting symptoms in Morquio A

Common initial presenting symptoms in Morquio A

n = 326 subjects

International Morquio A Registry

MPS
• Spinal stenosis with or without cord compression, has been reported in a small group of rapidly progressing MPS VI patients as a “typical” finding, with cord compression developing in 6 of them. (Thorne, 2001)

• The frequency of cervical myelopathy with atlantoaxial instability or spinal cord compression in patients with MPS VI is unknown. These are rarely reported abnormalities that are possibly underdiagnosed. (Giugliani 2007)
The Problem:

In children with Mucopolysaccharidosis (MPS),

- **Cervical Spinal instability** follows atlantoaxial subluxation due to ligamentous laxity and odontoid hypoplasia.

- **Progressive compression** is a result of deposition of glycosaminoglycans (GAGs) in ligaments, joints and dura; In some MPS types an underlying **short thickened posterior arch of C1** adds to the compression.

- Most patients develop both with varying severity. **Repetitive micro-concussion injury** more likely to occur when **instability and compression co-exist.**
Questions => Objectives

1. There are currently no studies detailing the timing of progression from spinal instability and/or compression to myelopathy

   We aim to evaluate the natural history of progressive cervical spinal cord compression in MPS

2. Does this progression occur at the same rate in everyone?

   We evaluate clinical & radiological progression difference within the clinical cohort
Patients & Methods

- Retrospective review between January 2003-December 2014

- MPS IV (Morquio-Brailsford) => 20
- MPS VI (Maroteaux-Lamy) => 3
- MPS I (Hurler-Schie) => 1

- 24 children, 12 boys, 12 girls
  - Median age at diagnosis was 3.6 years
  - For boys => 3.9 years; for girls => 3.3 years
Methods

• Baseline status, radiological instability, compression and progressive reduction in the spinal canal was measured over time
  – We also evaluated for presence and progression of deformity

• Clinical parameters included neurological and functional testing
Spine: Normal

Image courtesy of Ralph Lachman, MD
Spine: Dysostosis multiplex

- Dens hypoplasia
- Platyspondyly
- Anterior beaking
- Posterior scalloping
- Thoracolumbar kyphosis

Solanki et al, *J Inherit Metab Dis*, 2013
The “normal” Paediatric Cervical spine

• The median Torg ratio is 1.47 for both males and females primarily, and it reaches values of 1.06 for males and 1.10 for females by maturity.

• The anterior arch of the first cervical vertebra had ossified in 33% of the children by the age of three months and in 81% of the children by the age of one year.

• Closure of the synchondroses was completed in all children by the age of three years.
Cervical spine measurements: Meta-analysis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Instrumentation</th>
<th>N</th>
<th>Vertebral-Body Mean (SD)</th>
<th>Spinal-Canal Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tierney et al (2002)†</td>
<td>Magnetic resonance imaging scans</td>
<td>14</td>
<td>17.70 (2.18)</td>
<td>13.28 (1.47)</td>
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<tr>
<td>Torg et al (1996)‡</td>
<td>Radiographs</td>
<td>105</td>
<td>19.31 (1.86)</td>
<td>18.74 (1.84)</td>
</tr>
<tr>
<td>Herzog et al (1991)⁹†</td>
<td>Radiographs</td>
<td>80</td>
<td>17.70 (1.53)</td>
<td>15.14 (1.36)</td>
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<tr>
<td>Matsuura et al (1989)¹⁵†</td>
<td>Computed tomography scans</td>
<td>100</td>
<td>NR</td>
<td>14.09 (1.58)</td>
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<tr>
<td>Pavlov et al (1987)⁷‡</td>
<td>Radiographs</td>
<td>49</td>
<td>NR</td>
<td>18.89 (0.19)</td>
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<tr>
<td>Stanley et al (1986)¹⁶†</td>
<td>Computed tomography scans</td>
<td>52</td>
<td>NR</td>
<td>14.30 (0.34)</td>
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<tr>
<td>Hashimoto and Tak (1977)⁹†</td>
<td>Radiographs</td>
<td>48</td>
<td>NR</td>
<td>13.66 (1.09)</td>
</tr>
</tbody>
</table>

Spinal canal Mean ~ 14mm

Cervical Spine Stenosis Measures in Normal Subjects
Ryan T. Tierney; Catherine Maldjian; Carl G. Mattacola; Stephen J. Straub; Michael R. Sitler, *Journal of Athletic Training* 2002;37(2):190–193
Changes of cervical spinal cord and cervical spinal canal with age in asymptomatic subjects
(www.nature.com)
Radiological Values for stenosis

- Torg Ratio < 0.8 indicative of canal stenosis

- Space available for cord
  - < 1/3 of spinal canal space indicative of canal stenosis

- Surface area of cord in teenagers:
  - Mean Cord surface area was 91.8+9.7 mm$^2$ in males and 95.2+8.0 mm$^2$ in females
Measurement of Instability

- ADI > 5 mm is abnormal
- ADI > 8 mm suggests need for surgical management
- PADI < 14 mm implies stenosis and compression
- ... but these measurements are from adults
Results

• Radiological instability and compression were present in 83%,

• Radiological deformity in 54%.

• Speed and severity of progression varied.

• Half of children underwent surgery.
  – We compared differences between these two groups
  – Group A (Surgery), Group B (No surgery)
Spinal Deformity in MPS IV: Neck

Early, Intermediate and Late
Spinal Deformity in MPS: Spine

Early, Intermediate and Late
Appearance of the advanced MPS spine
Results: Time to Progression

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (Operated)</th>
<th>Group B (Conservative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instability</td>
<td>19</td>
<td>51</td>
</tr>
<tr>
<td>Cord Compression</td>
<td>11</td>
<td>43</td>
</tr>
<tr>
<td>CSF signal loss</td>
<td>21</td>
<td>51</td>
</tr>
<tr>
<td>Cord Signal Change</td>
<td>31</td>
<td>79</td>
</tr>
</tbody>
</table>

Time to progression in months
Discussion

• What are normal values in this population?

• Best modality to evaluate progression?

• Ideal time for surgery?
Canal Body Ratio: MPS VI vs normals?

- There is no published data yet.
- Preliminary study at BCH ongoing.
- Results suggest a 4 fold reduction in canal body ratio (sample size limited)
MPS VI vs. Normal Data

Change to Torg Ratio following surgery

- Male MPS VI
- 3m post-op
Conclusion:

- The radiological progression of spinal cord compression falls into two distinct groups.

- These findings correlate with clinical disease pattern, identify genotype-phenotype sub-groups and indicate the optimal window for intervention.

- We propose that this should ideally be at the stage of loss of CSF signal before development of cord compression and signal change within the cord in these children who have already compromised spinal cord perfusion due to concomitant systemic disease.
Current Strategy Summary

• If Compression alone:
  – Perform posterior decompression

• If instability alone:
  – Perform a C1-C2 or Occipito-cervical fixation

• If combined Compression & Instability
  – Perform Fixation and decompression

• If Deformity:
  – Perform deformity correction for scoliosis, kyphosis or kyphoscoliosis
Acknowledgements

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• Neurosurgery & Spinal Surgery Team
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• Our brave children that make it all worthwhile
Thank You !