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Orthopedic Aspects of Spinal Muscular Atrophy: Evolving Treatments in the Age of Disease Modifying Therapies

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Disclosures

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• “Quantification of muscle stiffness in spastic hemiplegic cerebral palsy using magnetic resonance elastography

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• “Muscle Stiffness in Cerebral Palsy: The Effect of Botulinum Toxin”

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• None

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Spinal muscular atrophy

- Relatively common
  - 1/6000-1/10,000
- Autosomal recessive
- Progressive neuromuscular disorder
  - Spectrum of functional impairment, age of onset
- Spinal cord anterior horn cells affected
  - Low muscle tone, no reflexes
  - Proximal weakness, lower > upper extremity
  - Respiratory muscles involved
Survival motor neuron (SMN) protein

- Important for neuronal development

**SMN1 gene involvement**
- SMN protein affected
- Anterior horn cell degeneration

**SMN2 gene**
- Much less viable SMN protein (5-10% of normal)
- SMN2 Copy number important, more protein
- Generally, Type I: <2 copies, Type II, III: ≥3 copies

**Disease-modifying agents target these genes**
- Nusinersen, Risdiplam, Onasemnogene abeparvovec
**TYPE I - Acute Infantile**

Onset: birth - 6mos
- Floppy baby
- Severe motor delay
- Can’t sit independently
- Improved respiratory function with gene Rx

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**TYPE II - Chronic Infantile**

Onset: 6-18mos
- Head control / sitting ok
- Wheelchair mobility
- Improved ambulatory function with gene Rx
Type III Kugelberg-Welander

Onset: 2 - 15 yrs
- Hip extensor weakness
- Trendelenburg gait
- Lumbar lordosis
- Crouch/Knee hyperextension (quads weakness)
- Wheelchair as adults
- Near normal lifespan

Orthopedic Rx non-controversial
Disease-modifying agents (DMAs)

• **Nusinersen (Spinraza™)**
  - Delivered by lumbar puncture or *tunnelled port*
  - Modifies **SMN2** gene splicing
  - More SMN2 = more SMN protein
  - Improved survival and motor development
  - *Risdiplam* (oral)

• **Onasemnogene abeparsovec (Zolgensma™)**
  - Replaces the defective **SMN1** gene
  - Similar improvements in function

These agents have changed the way Orthopedists think about SMA
Hammersmith Functional Motor Scale

- Validity and reliability confirmed for SMA, developed primarily for Types II, III
- 66 max total score
- Has been correlated with SMN2 copy #, FVC, muscle strength
- Used to document functional change after DMA Rx
Orthopedic Aspects of SMA

- **Scoliosis**
  - Seating imbalance
  - Standing/walking impairment
  - Respiratory dysfunction (?)

- **Hip instability**
  - Painful arthritis
  - Standing/walking impairment

- **Fractures**
  - Bone fragility
  - Tibia/femur most common
Orthopedic Aspects of SMA

- **Gait abnormalities**
  - Traditionally Type III
  - With Disease modifying agents, Type II
  - Lower extremity muscle contractures
  - Hip instability

- **Standing impairment**
  - Types I and II
  - Lower extremity muscle contractures
  - Hip instability/scoliosis

DMA Rx is changing attitudes...focus on function
Scoliosis in SMA

- Very common
  - 60-90% Type I/II
- Earlier onset than idiopathic cause
  - 7-8 years-old
- Proportional to functional level
  - DMAs likely having an impact
- Seating problems
- Difficult with care giving
- Respiratory decline concurrent

Double-major curve
Type II SMA
Bracing for Scoliosis in SMA

• Seating support
• Does not improve scoliosis
• Can exacerbate respiratory dysfunction
• Abdominal cutout for G-tube, breathing
• Semi-rigid best

Curves > 50-60° indicated for surgery

Goals of Scoliosis Surgery in SMA

- Comfortable SEATING
- EASE OF CARE-GIVING
- SOCIAL INTERACTION
- Decrease pain
- Benefits > Risks

DMAs improving function, decreasing risk
Types of scoliosis surgery

- Growth-friendly < 8 years-old
- Definitive fusion > 10 years old

8-10: individualized Rx

Leave a window for intrathecal access
Nusinersen access after spinal fusion: Options

• Laminectomy (L3) for intrathecal access
  • Clips at spinous process of L2/L4 for IR easy visualization for intrathecal access

• Convert to oral Risdiplam (Evrsdi®)

• Intrathecal catheter port
Preliminary Safety and Tolerability of a Novel Subcutaneous Intrathecal Catheter System for Repeated Outpatient Dosing of Nusinersen to Children and Adults With Spinal Muscular Atrophy

Kevin A. Strauss, MD,* Vincent J. Carson, MD,* Karla W. Brigatti, MS, LCGC,* Millie Young, RNC,* Donna L. Robinson, CRNP,* Christine Hendrickson, RNC,* Michael D. Fox, MD,†‡ Robert M. Reed, MD,§ Erik G. Paffenberger, PhD,* William Mackenzie, MD,* and Freeman Miller, MD,*¶

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Dr. Freeman Miller
For children who walk: consider not fusing to the pelvis for pelvic motion preservation
Chest deformity in SMA

- Bell-shaped chest
  - Intercostal muscle weakness
  - Relatively strong diaphragm
  - Ribs sag, lack of support
  - Respiratory decline over time

- Does scoliosis surgery help?
  - Not addressing the primary problem
  - Respiratory decline can vary with age
  - Prior studies not controlled

Chicken, egg, or two different chickens?
Chest gets worse despite early scoliosis surgery
The impact of scoliosis surgery on pulmonary function in spinal muscular atrophy: a systematic review

Abduljabber Alhammad1,2,3 • Yahya Othman3 • Ron El-Hawary4 • William G. Mackenzie5 • Jason J. Howard5

<table>
<thead>
<tr>
<th>Evidence-based Statement</th>
<th>GRADE Recommendation</th>
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<tbody>
<tr>
<td>Surgery is most often associated with decreases in pulmonary function</td>
<td>C</td>
</tr>
<tr>
<td>The impact of surgery on pulmonary function is variable but does not reliably improve over pre-operative baseline</td>
<td>C</td>
</tr>
<tr>
<td>Surgery may result in a decreased rate of decline in pulmonary function post-operatively</td>
<td>C</td>
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</tbody>
</table>

GRADE C – poor or conflicting evidence based on level IV/V evidence.
Growth Friendly Surgery for scoliosis in SMA

Prior to Nusinersen/gene therapies, children with Type I SMA often not surgical candidates due to operative risk.

Along with better pulmonary and critical care, reduced complication rates and longer lifespan.

Scoliosis causes pain, sitting imbalance, like any other NM diagnosis.

Scoliosis surgery can help:

Magnetically controlled growing rods optimal for low tone…conversion to definitive fusion not always needed.

13yoF w/ Type I SMA
Progressive scoliosis
Hip pain
Prevalence of Scoliosis in SMA

- Overall prevalence: 52%
- *Age at scoliosis onset:*
  - Overall: 7.1 (±2.3) y
  - Rises with SMA type

Prevalence of Scoliosis in SMA

- Type I: 68.7%
- Type II: 50.0%
- Type III: 21.4%

(*Ulusaloglu, Howard et al, POSNA 2023*)
Risk factors for Scoliosis in SMA

- Overall prevalence 52%
  - Age of onset: 7.2 years-old
  - 34(SD:22)° to 48(SD:29)° over 7y FU

### Proxies of disease severity (non-ambulatory)
DMA treatment did not prevent scoliosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate</th>
<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>p</td>
<td>Exp (B)</td>
</tr>
<tr>
<td>SMN2 &lt;3 copy</td>
<td>.029*</td>
<td>2.899</td>
</tr>
<tr>
<td>SMA type 1</td>
<td>.006*</td>
<td>8.067</td>
</tr>
<tr>
<td>SMA type 2</td>
<td>.076</td>
<td>3.667</td>
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<tr>
<td>DMA treatment</td>
<td>.066</td>
<td>0.335</td>
</tr>
<tr>
<td>Non-ambulatory, FMS$_{50}$=1</td>
<td>.039*</td>
<td>3.378</td>
</tr>
<tr>
<td>Hip displacement</td>
<td>&lt;.0.001*</td>
<td>10.303</td>
</tr>
</tbody>
</table>

(Ulusaloglu, Howard et al, POSNA 2023)
Hip instability in SMA

- **Hip instability is common in most neuromuscular disorders**
  - Cerebral palsy (CP) being the most studied
  - Also highly prevalent in SMA, linked to functional level

- **Hip abductor weakness, lack of functional weightbearing**

- Leads to laterally directed growth of the proximal femur (ball), acetabulum (socket) dysplasia

- **Eventual dislocation, osteoarthritis**
  - BUT variable outcomes in prior studies, small numbers.
  - Recent studies show higher pain prevalence than previously thought (58%)

*(Xu et al, JPO 2022)*
Hip Pain in SMA

- Risk Factors
  - Obesity
  - Prior scoliosis surgery with fusion to pelvis
  - Hip contractures
  - Hip dislocations

- Higher pain with ↑SMN2 copies, Type II > Type I
  - Better function, more strength

- Impact of DMAs on hip pain unknown
  - Higher function may lead to more pain (muscle force)

*(Hanna et al JBJS OA 2023; Xu et al, JPO 2022)*
Type I SMA with progressive hip displacement

2 years-old  5 years-old  7 years-old

Usually painless until later, not all develop pain
SMA hip instability: X-ray features

- **Growth plate tilt (*)&nbsp;**
  - Ball tilts laterally
  - ‘Coxa valga’
  - Pressure on the socket (**) 

- **Acetabular dysplasia**
  - Progressive
  - Lack of support (roof)
  - **Dislocation**
Type II SMA, Nusinersen, able to walk

Indications for surgery: Pain, walkers, DMA treatment?
Direct the ‘ball’ into the socket
Reshape the hip socket
SMA hip instability: Surgical Treatment

Prevent arthritis, improve seating, improve positioning/perineal care
Risk factors for Hip Instability in SMA

- 82 patients with SMA, Nemours Muscle Clinic
  - Type I: 39%, II: 44%, III: 17%

- Hip surveillance X-rays

- Risk factors investigated
  - Genetic severity (# of SMN2 copies)
  - SMA Type
  - DMA Treatment > 2 years (mostly Nusinersen)
  - Walking status
  - Hammersmith Motor Scale (66 max score)
  - Presence of Scoliosis (>40°)

Hip surveillance X-ray with MP measurement

(Ulusaloglu, Howard et al, POSNA 2022)
Prevalence of hip displacement in SMA

(Ulusaloglu, Howard et al, AACPDM 2022)

<table>
<thead>
<tr>
<th>SMA Type</th>
<th>Prevalence</th>
<th>*Age at HD onset:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>84%</td>
<td>3.1yo</td>
</tr>
<tr>
<td>II</td>
<td>80%</td>
<td>5.8yo</td>
</tr>
<tr>
<td>III</td>
<td>36%</td>
<td>9.0yo</td>
</tr>
</tbody>
</table>

- Overall prevalence: 75.6%
- Age at HD onset: 4.6 (SD: 2.7) years
Risk Factors for Hip Displacement

- Independant risk factors
  - SMA Type II (OR: 6.2)
  - Scoliosis (OR: 9.7)

- DMA Rx not protective
  - 66 (80%) patients w/ DMA
  - 64% Nusinersen

Hammersmith Score > 23 was protective

DMA treatment did not prevent hip instability
Should we treat hip Instability in SMA?

• We know the risk factors

• Prior studies on SMA hips controversial (except Type III)
  • No DMA Treatment
  • Poor outcome measures
  • Better medical management now

• DMA treatment influential
  • Patients are stronger
  • More ambulatory
  • Can better tolerate bigger surgeries

Although DMA treatment does not seem to prevent hip instability, increased function reported to lead to higher risk of moderate to severe pain*

Pre-op bisphosphonates, especially for Type I

*(Hanna et al, JBJS OA 2023; Xu et al, JPO 2022)
Will we see more of this after DMA treatment?
Guided growth may provide a low-risk Hip Rx

NEWER MINIMALLY INVASIVE OUTPATIENT Rx
USED IN CEREBRAL PALSY
MAY HOLD PROMISE FOR SMA AS WELL
Muscle Contractures in SMA

• **Muscle imbalance**
  - Tight heel cords (equinus)
  - Knee flexion contractures
  - Hip flexor/adductor > abductor contractures

• **Lower > upper limbs**
  - Tight heel cords (equinus)
  - Knee flexion contractures
  - Hip flexor/adductor > abductor contractures

• **Foot deformities**
  - Equinovarus ('clubfoot')
  - Planovalgus ('flatfoot')
  - Toe flexor contractures

Contractures worsen by SMA Type and with age...braces may delay but not prevent
The Foot as a lever

The right brace can turn a flexible foot deformity into a stable lever
Goals of Muscle Contracture Surgery in SMA

• **Improve sitting**
  - Wheelchair seating

• **Improve standing**
  - Traditionally Type II
  - With Disease modifying agents, Type I

• **Improve walking**
  - Traditionally Type III
  - With Disease modifying agents, Type II
  - Orthotic/shoe fitting

DMA Rx is changing attitudes...focus on function
INCREASING SURGICAL DOSE

“Strayer” Gastrocnemius Recession

Slide Lengthening TAL
- Double hemisections — White
- Triple hemisections — Hoke

Z Lengthening TAL (Open)

Heel Cord Advancement (HCA)

Courtesy HK Graham
RCH Melbourne
Crouch gait after heel cord lengthening (CP)

Quads weakness in SMA, risk of losing walking ability

Needs to be “low dose” surgery
Knee flexion contractures limiting gait

10 year-old F Type II SMA, early Nusinersen trial, walking
Progressive knee flexion contractures
Physical Examination

<table>
<thead>
<tr>
<th></th>
<th>PASSIVE ROM</th>
<th>STRENGTH</th>
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<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Hip Flex</td>
<td>125</td>
<td>140</td>
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<tr>
<td>Hip Ext</td>
<td>-15</td>
<td>15</td>
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<tr>
<td>Hip Abd</td>
<td>28</td>
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<tr>
<td>Hip Int Rot</td>
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<tr>
<td>Ely Test</td>
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<tr>
<td>Dorsi (flex)</td>
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<td>15</td>
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<tr>
<td>Dorsi (ext)</td>
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<td>60</td>
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<tr>
<td>Ankle Inv</td>
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<td>60</td>
</tr>
<tr>
<td>Ankle Ever</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>TMA</td>
<td>30 EXT</td>
<td>15 EXT</td>
</tr>
</tbody>
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5 years-old

10 years-old

Progression in muscle contractures
- Knee
- Hip

Some decrease in strength around the hip but otherwise preserved/improved
Knee flexion contractures limiting gait (braces)

Better with braces but knee flexion requires quads activation = fatigue
Guided growth: gradual correction, easier rehabilitation

Growth plate tether
- Anterior (front)
- Untethered at the back

Gradual improvement over time
- 1° per month
- Weightbearing
- Easier rehab than bony osteotomy

Minimize immobilization, early weightbearing and ambulation are key after surgery
Case: 9yo M, MMC, Diastomatomyelia w/ 30° fixed knee contracture

Immediate postop

Time for screw removal WHEN DEFORMITY CORRECTED or when end of growth

2 years postop
Peri-operative considerations

• **Respiratory optimization**
  • Pulmonary function tests essential
  • Pneumonia/Resp failure risks
  • Related to SMA Type

• **Nutritional optimization**
  • Reduces infection risk
  • Improves wound healing

• **Bone health optimization**
  • Bone Density (DEXA) scan
  • Need strong bone to hold implants
  • Reduces risk of fracture
  • Consider bisphosphonates, especially for Type I

Type I SMA
DEXA scan distal femur
Solid Ankle-Foot Orthosis (SAFO)

- GRF: augmented, in front of knee
  - CROUCH, minimal knee FC
- Appropriate for SMA walkers when soleus/quads weak
- Corrects flexible foot deformity
- Requires ankle DF to at least 0 deg
- Stair climbing more difficult
- Better tolerated than GRAFO

Focus on function:
Different patients need different braces
Summary

- Disease-modifying agents (DMA) targeting SMN1 and SMN2 genes improve function in SMA
- Orthopedic problems seem to develop despite DMA treatment
- DMA treatment improves medical aspects of SMA, allowing safer surgeries
- Given improvements in strength with DMA treatment, hip arthritis may become a bigger problem
- Scoliosis surgery for functional goals and quality of life, not pulmonary function
- Surgical decision-making should focus on functional goals and surgical “dose”

Medical literature lagging behind advances in SMA gene Rx... Need more studies to determine orthopedic outcomes in this new era