Effect of EOS Severity and Treatment on Pulmonary Function Relative to Stature (as Represented by Pelvic Width) in Children with SMA

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Disclosures

- Brian Snyder and Robert Graham are on the Board of CURESMA
- Brian Snyder and Robert Graham are consultants to BioGen
SMA: Most Common Monogenic Cause of Infant Death

- Progressive debilitating neuromuscular disease characterized by degeneration spinal motor neurons → atrophy of skeletal muscle
- Mutations or deletions \( SMN1 \) gene (exon 7 and/or 8) chromosome 5q
- Extent of clinical involvement depends on copies of SMN2:
  - \( \leq 2 \) copies more severe disease; 3-4 copies milder disease

Incidence: ~1 in 11,000 live births
Carrier frequency: ~1 in 40

Unaffected

\[ \text{SMN1} \quad / \quad \text{SMN2} \]

- Functional SMN protein
- Mostly non-functional SMN protein

DNA

SMA

\[ \text{SMN1} \quad / \quad \text{SMN2} \]

- Mostly non-functional SMN protein

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SMA, spinal muscular atrophy; SMN1, survival motor neuron 1.
## SMA Classified According to:
### Age of Onset and Spectrum of Clinical Severity

<table>
<thead>
<tr>
<th>Type I (severe - ≤ 2 copies SMN2)</th>
<th>Type II (intermediate - &gt; 2 copies SMN2)</th>
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</thead>
<tbody>
<tr>
<td>• Most common</td>
<td>• Onset at 6–18 months</td>
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<tr>
<td>• Onset at &lt; 6 months</td>
<td>• Can sit without support but progressive muscle atrophy (proximal &gt; distal muscles)</td>
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<tr>
<td>• <strong>Never sits</strong></td>
<td>• <strong>Never stands</strong></td>
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<tr>
<td>• Areflexia = Classic ‘floppy’ infant</td>
<td>• Tongue fasciculation</td>
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<td>• Bulbar denervation, tongue fasciculation</td>
<td>• Variable bulbar and respiratory weakness</td>
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<tr>
<td>• Swallowing and feeding difficulties</td>
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<td>• Respiratory insufficiency</td>
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<table>
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<tr>
<th>Type III (mild - 3-4 copies SMN2)</th>
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<tr>
<td>• Onset at &gt; 18 months</td>
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<tr>
<td>• Proximal symmetrical weakness</td>
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<tr>
<td>• <strong>Stands and walks,</strong> but may need wheelchair or lose ambulation during adolescence</td>
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<td>• Weak or absent tendon reflexes</td>
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Clinical Problem

**Early Onset Scoliosis → Thoracic Insufficiency**

- Types 1 and 2 associated with progressive spine and thoracic (parasol rib) deformity
  - Contributes to Restrictive lung disease and respiratory dysfunction
- Cobb angle alone does not predict extent of respiratory deficiency
  - Fails to account for chest wall deformity and interference with pulmonary growth
Treatment of Scoliosis

(Cobb ≤ 50°)
- Bracing (TLSO) slows progression
  - does not decrease ultimate need for surgical correction

(Cobb > 50°)
- **Skeletal age <8 y/o:**
  - Posterior, Non-fusion “growing rods” (VEPTR, MAGEC, Luque Trolley)
- **Closed tri-radiate:**
  - Posterior multi-segmental instrumentation + spine fusion
  - Instrumentation to pelvis provides better control of “crank-shaft” & pelvic obliquity

Growing Rods < 8 y/o

Instrumented Spine Fusion
Closed tri-radiate
Pulmonary Function

- PFTs reported as %tiles based on height (standing, sitting, spine)
- Traditional 2D measures of thoracic volume and spine length that predict pulmonary function are difficult to evaluate in SMA because of skeletal deformity (scoliosis, contractures)

Sriram Balasubramanian
Normal Male=25, Female=42
Pelvic Inlet Width (PIW)

• PIW correlates with spine height and stature with growth
  – independent of disease or age
  – PIW reliably measured on spine and/or hip X-rays

➢ Surrogate for thoracic height in EOS
Hypothesis

1. Pulmonary function as represented by FVC varies proportionately with stature (thoracic height).

**Scoliosis affects this relationship:**
- ✓ children with mild/moderate scoliosis (Cobb angle ≤50°) *follow* this relationship
- ✓ children with more severe scoliosis (Cobb angle >50°) *do not*

2. Correction of scoliosis by spinal instrumentation partially restores this relationship

➢ Therefore, we evaluated whether FVC varies proportionately with stature, *as represented by PIW*, and whether this relationship was affected by EOS severity or treatment (TLSO, spinal instrumentation)
Methods

• Cohort
  – 53 SMA pts. types: Type 1 (2%), Type 2 (53%), Type 3 (45%)
  – Analyzed over 5.2 yrs. (SD 2.8; range 1.1-11.6 yrs).
  – Nearly all received Nusinersin via lumbar puncture

• Treatment
  – Cobb ≤ 50° Rx = TLSO
  – Cobb > 50° or unresponsive to TLSO, Rx = GR (age ≤10 yr) or PSF (closed tri-radiate)

• Analysis (Bi-annual)
  – Bedside Forced Vital Capacity
  – Sitting spine X-ray in/out of TLSO or after Growing Rod insertion/lengthening

  ☐ Cobb, PIW, FVC @ initiation treatment (TLSO, GR) compared to last follow-up
Results: PIW vs FVC

• At Presentation
  – Cobb $\leq 50^\circ$: variability in PIW accounts for 74% variability in FVC
    $(r = 0.86; p<0.001)$
  – Cobb $>50^\circ$: no correlation ($p=0.27$)

IMPLIES: SMA children with moderate spinal deformity, pulmonary function varies proportionately with change in stature (i.e. growth)
However for severe scoliosis, the change in pulmonary function is disproportionate relative to change in stature = thoracic insufficiency
Results: 2-way ANOVA comparing FVC normalized by PIW

For treatment (TLSO vs GR) @ initiation vs last f/u, segregated by initial curve severity (Cobb >50° vs <50°)

- Underpowered, and Biased cohort – more severe curves treated surgically, less severe curves treated by TLSO

Indicates that surgical treatment for Cobb >50°, while scoliosis corrects by ~40%, even if Cobb corrected to <50°, it did not restore the proportionality between PIW and FVC;

Whereas for less severe spinal deformity treated by TLSO, even though curve progressed 10%, the proportionality between PIW and FVC was preserved
Conclusions

- The direct relationship between pelvic inlet width (PIW), a radiographic surrogate for thoracic height and forced vital capacity (FVC), a measure of pulmonary function indicates that for SMA children, age <18 yrs, with moderate spinal deformity (Cobb ≤ 50°) pulmonary function is able to change proportionately with the change in stature (growth).

- However for severe scoliosis (Cobb > 50°), pulmonary function was unable to change in relative proportion to the change in stature = thoracic insufficiency.

- Surgical treatment did not modify or restore this relationship because:
  - surgical intervention occurred too late, after intrinsic (and irreversible) changes to the thorax and lung parenchyma transpired;
  - increased thoracic stiffness, a consequence of altered ventilator mechanics induced by Parasol deformity of the thorax, tissue scarring, rigidity of surgical instrumentation, and/or failure of the surgical intervention to improve the projected surface area and excursion of the diaphragm.
Thank You

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