Session 3: Mini Symposium: Spinal Muscular Atrophy (SMA): Spine

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-Disclosures-

Warning: Science Coming!
What is Spinal Muscular Atrophy (SMA)?

- Incidence: ~1 / 10,000 live births; 30,000 Worldwide
- Leading causes of genetic mortality in infants and toddlers, though manifestations highly variable
Pathophysiology

• Progressive degeneration of alpha lower motor neurons in anterior horn cells of spinal cord

• Sensation and intelligence normal

• Proximal muscles affected first

• Diaphragm, GI muscles, and heart spared
Genetics of SMA

- Autosomal recessive
- Chromosome 5q13 locus
  - One copy of \textit{SMN1}
  - Variable number of copies of \textit{SMN2}
- SMN involved in controlling \textit{apoptosis}; keeps neurons alive
- Carrier frequency: 1/50
Multiple, but variable numbers of, copies of SMN gene in the human genome

- SMN1: Deleted in SMA
- SMN2: Variable Copy Number

Functional SMN protein

SMN protein

Truncated SMN protein (rapidly degraded)

~10% of SMN2 pre-mRNA is properly spliced and subsequently translated into full length SMN protein.

Lunn et al. Lancet 2008; 371: 2120-2133
Types of Spinal Muscular Atrophy

Type 1 (Werdnig-Hoffmann, Infantile SMA)
  Most severe; little spontaneous extremity movement

Type 2 (Intermediate SMA)
  Can often sit without support, but can rarely stand

Type 3 (Kugelberg-Walander, Juvenile SMA)
  Ambulatory, but have weakness of the hip muscles

Type IV - Adult SMA; ambulatory
Scoliosis in SMA

• The severity and onset of scoliosis are directly related to the severity of SMA

• Type 1: 100% develop scoliosis
  ≤ 2 years of age

• Type 2: 100% develop scoliosis
  1-7 years of age

• Type 3: 50% develop scoliosis
  4-14 years of age
Scoliosis in SMA

- Can exacerbate pulmonary demise
- Role of Parasol
- Can lead to issues with seating, UE use, and comfort
- Can result or hasten hip dislocation
Goldman Sachs Group Inc. (GS) partner Dinakar Singh discovered in 2001 that his 19-month-old daughter, Arya, had a crippling genetic disease called spinal muscular atrophy.

The malady makes the nerve cells that control muscles gradually deteriorate. There are no treatments, let alone a cure, Bloomberg Markets magazine reports in its October issue. Worse still, while the gene causing the ailment had recently been discovered, nobody in the drug industry was doing much about it, he says.

“I was fearful and anxious that treatments would be developed, but far too late to save Arya,” says Singh, 42, who founded and runs New York hedge fund TPG-Axon Capital Management LP, which has $8.1 billion in assets. “We didn’t want to find out 25 years later that the science was really there but there isn’t a drug because nobody focused on it.”

Singh, who left Goldman in 2004, has spent almost $100 million of his own money to create and fund...
**ISIS-SMN\textsubscript{Rx}: Modulating Splicing of SMN2 to Increase Normal SMN Protein**

Must Be Given Intrathecally!

# Achievement of Motor Milestones in Some Infants

**Blue—6 MG, Red—12 MG**

<table>
<thead>
<tr>
<th>Head control</th>
<th>Unable to maintain upright</th>
<th>Wobbles</th>
<th>All the time upright</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting</td>
<td>Cannot sit</td>
<td>Sit with support at hips</td>
<td>Props</td>
<td>Stable sit</td>
</tr>
<tr>
<td>Voluntary grasp</td>
<td>No grasp</td>
<td>Uses whole hand</td>
<td>Index finger and thumb but immature grasp</td>
<td>Pincer grasp</td>
</tr>
<tr>
<td>Ability to kick (in supine)</td>
<td>No kicking</td>
<td>Kicks horizontally; legs do not lift</td>
<td>Upward (vertically)</td>
<td>Touches leg</td>
</tr>
<tr>
<td>Rolling</td>
<td>No rolling</td>
<td>Rolling to side</td>
<td>Prone to supine</td>
<td>Supine to prone</td>
</tr>
<tr>
<td>Crawling</td>
<td>Does not lift head</td>
<td>On elbow</td>
<td>On outstretched hand</td>
<td>Crawling flat on abdomen</td>
</tr>
<tr>
<td>Standing</td>
<td>Does not support weight</td>
<td>Supports weight</td>
<td>Stands with support</td>
<td>Stands unaided</td>
</tr>
<tr>
<td>Walking</td>
<td>No walking</td>
<td>Bouncing</td>
<td>Cruising (holding on)</td>
<td>Walking independently</td>
</tr>
</tbody>
</table>
Consider **Surgical Stabilization** for Progressive Curves Before They Get Too Large

### Etiology
- Congenital/Structural
- Neuromuscular
- Syndromic
- Idiopathic

### Cobb Angle (Major Curve)
1. <20°
2. 20-49°
3. 50-89°
4. ≥90°

### Maximum Total Kyphosis
- (-) <20°
- N: 21-49°
- (+): ≥50°

### Progression Modifier (optional)
- P0: <10°/yr
- P1: 10-19°/yr
- P2: ≥20°/yr

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**C-EOS Vitale et al.**
Optimal Window for Timing of Surgery?

- **Age**
- **Size of Curve**

Graph showing the relationship between vital capacity and increasing scoliosis over age, indicating the optimal window for surgery.

- **Vital Capacity**: Decreasing as age increases.
- **Scoliosis**: Increasing as age increases.

The graph suggests that surgery is appropriate in a specific window where vital capacity is decreasing and scoliosis is increasing.
Surgical Treatment Options for Progressive Curves in SMA

Growth Strategies
- MAGEC - TGR

Fusion
Patient TJ: 3 yo with Type I SMA

SMA Type 1

- 3 year old boy
- Gastrostomy Tube
- Ventilator dependent
- LE w/ decreased tone
- Arm Contractures
- Scoliosis Jacket 1 ½ y
- B/L VEPTRs to pelvis
Patient TJ – s/p VEPTR

Limitation with Amount of Proximal Rib Fixation
TJ

EOSQ 54 → 68
Patient JL

7 year old girl

SMA Type 2
Patient JL

Improvement in need for daytime respiratory support

Improvement in Secondary TIS?
Lengthening Procedures every 4-6 months
Not ideal
Parasol seems to happen despite *traditional* growing rods and also despite *traditional* VEPTR

Courtesy Livingston, Zurakowski, and Snyder, ICEOS 2014
3 yo Spinal Muscular Atrophy Type 1

- No BiPAP, but uses Cough Assist nightly
- G-tube
- Cobb 23° → 54° in 6 mo.
- C-EOS: N3+P2

Patient OK:
Will More Rib Support Slow Parasol?

- High Density Rib Fixation for SMA
Confronting the Realities of EOS Treatment

- too much uncertainty in indications
- too many complications
Conclusion - Early Onset Scoliosis

- Significant Challenge and Unsolved Problem
- Be vigilant, prepare for “obstacles”, have stamina!
- Every tool in our disposal
- Significant opportunities to improve care through Clinical Research
  - GSSG and CSSG
THANK YOU
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