Spinal Muscular Atrophy: Genotype and Phenotype

John Brandsema, MD
SMA Symposium
September, 2016
Spinal Muscular Atrophy (SMA)

- Leading Genetic cause of Infant Death
  - Autosomal Recessive
  - High Carrier Rate of approx. 1:50
- Degeneration of motor neurons in anterior horn
- Three clinical types in childhood
  - Spectrum

Malerba, KH et al *Phys Ther* (2013)
<table>
<thead>
<tr>
<th>SMA Type</th>
<th>Eponym</th>
<th>Age at Onset</th>
<th>Life Span</th>
<th>Highest Milestone Achieved</th>
<th>Proportion of Total SMA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Werdnig-Hoffman</td>
<td>Prenatal - 6 months</td>
<td>&lt;2 years without respiratory support</td>
<td>Never sits</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>Dubowitz</td>
<td>6-18 months</td>
<td>70% alive at 25 years</td>
<td>Sits independently - never stands</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>Kugelberg-Welander</td>
<td>&gt;18 months</td>
<td>Adulthood</td>
<td>Stands and walks</td>
<td>12</td>
</tr>
</tbody>
</table>

*Neuromuscular Disorders of Infancy, Childhood and Adolescence. (2nd edition, 2015)*
SMA and SMN1/SMN2

Healthy Person

SMN2

SMN2

SMN1

SMA Patients

Severity

SMN2

Copy #

1 Copy

SMN2

SMN2

SMN1

2 Copies

SMN2

SMN2

SMN1

3 Copies

SMN2

SMN2

SMN1

SMN2

SMN2 is a Disease Modifier
SMN Stability

Pre-mRNA

mRNA

Protein

Normal SMN protein levels

Low SMN protein levels

Splicing

Translation
Arch Neurol, 2011
Sensory degeneration?
Autonomic involvement?
Neuromuscular junction dysfunction?
Bulbar and brainstem involvement: weak cry, tongue fasciculation

Breathing difficulties

Cardiac autonomic involvement and congenital heart defects

Gastroesophageal reflux

Constipation, weight loss

Joint contractures

Decreased or absent deep reflexes

Muscular atrophy, weakness and hypotonia
Multisystemic in severe SMA

- **Heart/ vessels**
  - Arrhythmias
  - Cardiomyopathy
  - Vasculopathy

- **Liver**
  - Low IGF-1
  - Iron overload

- **Cognitive/ brain**
  - No IQ difference between SMA types or with controls
    - *Neuromusc Disord*, 2002
  - Migrational disorders
  - Thalamus
  - Hippocampus

*Trends Mol Med*, 2013
Management Questions: Nonsitters/ Type 1

- Tolerance of upright position
  - Bracing/ cutout/ band?
- Role for spinal surgery in “near-sitters”
- Nissen with Gtube
  - *J Child Neurol*, 2007
- Sensitivity to catabolic stress
  - Acute illness and perioperative management
- Synagis prophylaxis
  - Age change: <1 year
  - Canada: by weight
Management Questions: Sitters/ Type 2

- Timing and degree of respiratory support
  - Nocturnal hypoventilation
  - Frequent infections
- Scoliosis surgery – hip complications
- Underweight vs. overweight
  - Special diets
- Sensitivity to catabolic stress
  - Acute illness and perioperative management

http://emedicine.medscape.com/article/1264401
On the Horizon for SMA

Based on publicly disclosed timelines, January 2016
Thank you!