Spinal Muscular Atrophy
Historical Timeline

- **1891**: Werndig and Hoffmann describe SMA 1 (Arch Psych Nervenkrankheiten)
- **1956**: Kugelberg and Welander describe SMA 3 (Arch Neurol)
- **1990**: Gene localized to $5q11$ (Brzustowicz, Gilliam, Nature)
- **1990**: Disease causing and modifying genes identified (Lefebvre, Cell)
- **1995**: Human Trials
- **1995**: In vitro and animal studies
## Clinical Spectrum

<table>
<thead>
<tr>
<th>Type</th>
<th>Age at onset</th>
<th>Motor milestone</th>
<th>Life span</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA 0</td>
<td>prenatal</td>
<td>Never sit unsupported</td>
<td>&lt;6 months</td>
</tr>
<tr>
<td>SMA 1</td>
<td>0-6 months 0-3 months 3-6 months</td>
<td>Never sit unsupported</td>
<td>&lt;2 years</td>
</tr>
<tr>
<td>SMA 2</td>
<td>6-18 months</td>
<td>Sit at some time, but never walk independently</td>
<td>~70% alive at 25 years</td>
</tr>
<tr>
<td>SMA 3</td>
<td>&gt;18 months  &lt;3 years  &gt;3 years</td>
<td>Able to stand and walk at some time</td>
<td>Almost normal</td>
</tr>
<tr>
<td>SMA 4</td>
<td>&gt;21 years</td>
<td>Able to stand and walk at some time</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Clinical signs: anterior horn cell dysfunction

- Hypotonia
- Muscle weakness
- Arreflexia
- Fasciculations
Genetics

- 2nd most common recessive disease (1:6-10K live births)
- The most common fatal genetic disease in infants
- Carrier frequency 1:34
- Phenotypes distinguished based on highest motor milestone achieved
- Type 1 highest incidence
Genetics

- **Survival Motor Neuron gene mutation**
- SMN1 – telomeric copy
- SMN2 – centromeric copy
- Chromosome 5q12.2-q13.3
- Testing sent for:
  - SMN1 homozygous deletion, and
  - SMN2 copy number
Genetics

Unstable, rapidly degraded

Stable, normal SMN level
SMN2 copy number

Natural History of SMA type 1

Methods

• International SMA Patient Registry
• family-reported data from participants
• additional clinical information through a mail-in questionnaire.
• Survival
  ▫ Kaplan–Meier method and Cox proportional hazards models
  ▫ Age at death and age at death and ventilation >16 hours/day as the outcome.

The changing natural history of spinal muscular atrophy type 1. Neurology 2007
M Oskoui, G Levy, CJ Garland, JM Gray, J O’Hagen, DC De Vivo, P Kaufmann
Natural History of SMA type 1

Results

- N=143
- Model only YOB as a predictor
- 70% reduction in the risk of death
- HR 0.3, 95% CI 0.2–0.5, p<0.001) over a mean follow-up of 49.9 months
- Median time to death or BiPAP 16h/day
  - 7.5 months vs 24 months

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Natural History of SMA type 1

Results

- Model controlling for demographic and clinical care variables, YOB was no longer associated with age at death
- HR 1.0, 95% CI 0.6 –1.8, p=0.9.

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Natural History of SMA type 1

Results

- Significant effect in reducing risk of death:
  - NI ventilation for >16 h/d
  - use of M I-E device
  - Gastrostomy tube feeding

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at symptom onset, mo</td>
<td>0.6 (0.5–0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventilation &gt; 16 h/d†</td>
<td>0.3 (0.1–0.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>MI-E device</td>
<td>0.2 (0.1–0.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Gastrostomy tube feeding</td>
<td>0.5 (0.3–1.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Amino acid diet</td>
<td>0.4 (0.2–1.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>YOB, 1995–2006 vs 1980–1994</td>
<td>1.0 (0.6–1.8)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

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Observational Study of SMA Type I and Implications for Clinical Trials

- Prospective longitudinal study
- 3 sites: Columbia, Boston Children’s, CHOP
- 34 of 54 eligible SMA 1 subjects enrolled (63%)
- Combined endpoint: death or requiring at least 16 hours a day of non-invasive ventilation support
- All had genetic confirmation of homozygous exon 7/8 deletion of SMN1 gene on chromo 5q

Finkel et al, Neurology 2014
Survival by clinical subtype

Causes of death:
- Acute pulmonary infection (6)
- Airway obstruction (2)
- Bradycardic arrest (1)

Finkel et al, Neurology 2014
Combined endpoint survival

Median for 1B: 11.9 (IQR 7.0-22.0)
Median for 1C: 13.6 (IQR 8.8-20.1)

Finkel et al, Neurology 2014
Survival by SMN 2 copy number

Median age for 2 copies: 10.5 (IQR 8.1-13.6)
25th %ile for 3 copies: 22.0

Finkel et al, Neurology 2014
Prospective cohort study of spinal muscular atrophy types 2 and 3

- Prospective longitudinal study
- 3 sites: Columbia, Boston Children’s, CHOP
- Enrolled 79 children
  - 41 with SMA type 2 (all 3 copies SMN 2)
  - 38 with SMA type 3 (53% with 3 copies SMN 2)
- All had genetic confirmation of homozygous exon 7/8 deletion of SMN1 gene on chromo 5q

Kaufmann et al, Neurology 2012
Key finding #1

- Slow functional declines in motor strength and pulmonary function when observed over 1 year

Kaufmann et al, Neurology 2012
Key finding #2

- Children consistently rated their physical and total quality of life higher than their parents.
- The health related quality of life relatively stable over time.

Kaufmann et al, Neurology 2012
Quality of Life

- Perception of poor QoL for children with SMA 1 not necessarily shared by their care providers

- Self-reported QoL has no correlation with functional status
  - de Oliveira CM, Araújo AP. Self reported QOL has no correlation with functional status in children and adolescents with SMA. Eur J Paeditra Neurol 2011;15 (1):36-9
New treatments/cure on the horizon

- Antisense oligonucleotide drugs designed to alter splicing of SMN2 mRNA, increasing the amount of functional SMN protein produced
- Promising results from phase 2 trials in SMA type 1 and 2

Finkel et al, Neurology 2014
Consensus statement for standard of care in SMA. Wang et al, J child Neurol 2007