Spinal Muscular Atrophy: Updates in diagnosis and management

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Objectives

- What is SMA?
  - Pathophysiologic and genetic mechanisms
  - How to identify a case of SMA

- What can be done?
  - Review of advances in standards of care and treatment
  - Detailed review of treatment available regionally

- What to do if you have a suspected case?
  - How to refer a patient?
  - How to counsel a patient/ family?
  - Urgency of referral
What is Spinal Muscular Atrophy?

- Autosomal recessive pediatric onset neurodegenerative disease
- Deletions (mutation) in 5q13 SMN1 gene ‘Survival of the motor neuron gene’
  
  ![Genetic Location](https://ghr.nlm.nih.gov/gene/SMN1#location)

- SMN protein is important for motor neuron health and survival
  - Progressive loss of alpha motor neurons in the anterior horn cell of spinal cord

- Incidence 1:10,000

- Carrier frequency about 1:35 in the Caucasian population **
  - ** May be even higher because we may miss:
    - Asymptomatic individuals
    - Embryonic lethal subjects

Images:
www.clinicalgate.com
https://ghr.nlm.nih.gov/gene/SMN1#location
Exon 7 not recognized by splicing machinery
Get SMN2Δ7 transcripts

Truncated SMN protein (only 282 aa) is unstable and nonfunctional

**SMN2 gene allows for rescue (from embryonic lethality)**
Less efficient = each copy produces about 10-15% full length protein compared to SMN1 gene
### SMA Subtypes

The more SMN2 copies you have, the better....

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
<th>SMN2 Copy</th>
<th>Age Onset</th>
<th>Max Motor</th>
<th>Survival</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;1 %</td>
<td>1</td>
<td>Prenatal</td>
<td>Never sit</td>
<td>&lt; 6 mo</td>
<td>Respiratory failure, Dysphagia, Contractures, Decreased fetal movement</td>
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<tr>
<td>1</td>
<td>50–60 %</td>
<td>2,3</td>
<td>0–6 mo</td>
<td>Never sit</td>
<td>&lt; 2 yr</td>
<td>Respiratory failure, Dysphagia, Weak cough, Paradoxical breathing, Contractures, Severe weakness</td>
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<tr>
<td>2</td>
<td>30 %</td>
<td>2,3,4</td>
<td>&lt;18 mo</td>
<td>Sit</td>
<td>&gt; 2 yr/Adult</td>
<td>Respiratory insufficiency, Weak cough, Tremor, Scoliosis, Contractures, Weakness</td>
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<td>3</td>
<td>10 %</td>
<td>3–4</td>
<td>18 mo – 21 yr</td>
<td>Walk</td>
<td>Adult</td>
<td>Variable weakness, Joint contractures, Scoliosis</td>
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<tr>
<td>4</td>
<td>1 %</td>
<td>4+</td>
<td>Late childhood-Adult</td>
<td>Walk</td>
<td>Adult</td>
<td>Mild weakness</td>
</tr>
</tbody>
</table>

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*Image not provided.*
SMA Type 1 (Werdnig-Hoffman Disease)

- Disease onset – within first 6 months of life
- Muscle weakness, hypotonia, areflexia – in limbs and trunk
- Clinical course:
  - Impaired head control (neck weakness)
  - Unable to sit or walk
  - Weak cry and cough
  - Difficulty with swallowing, feeding, and handling of oral secretions (before 1 year of age)
  - Die (or require > 16 hrs respiratory support) within first 2 years of life – due to bulbar dysfunction or pulmonary complications
SMA Type 2

• Intermediate Form

• Symptom onset after 6 months old

• Clinical Course:
  – Achieve sitting, but never able to walk unaided
  – Bulbar weakness; swallowing difficulties – can lead to poor weight gain
  – Intercostal muscle weakness → weak cough, difficulty clearing secretions
  – Fine tremors with extended fingers or when attempting hand grips
  – Kyphoscoliosis develops – requiring bracing or spinal surgery
  – Joint contractures over years
  – Lack of DTRs in about 70% of patients
  – Survival > 2 years

SMA Type 3 (Kugelberg-Welander Disease)

- Able to sit and walk (some lose ability to walk in childhood)
- Presenting Features:
  - Difficulties ascending and descending stairs at 2-3 years of age
  - Proximal Muscle weakness
  - Lower extremities more severely affected than upper extremities
  - Reduced or absent DTRs

- **Onset < 3 years – Type 3a**
  - 44% maintained walking by age 20 years
  - 22% maintained walking by age 40 years

- **Onset > 3 years – Type 3b**
  - 90% maintained walking by age 20 years
  - 58% maintained walking by age 40 years

- Scoliosis can develop
- Swallowing, cough, and nocturnal hypoventilation (may occur)
- Muscle aches and joint overuse symptoms are common

Spinal Muscular Atrophy: 
Making the Diagnosis
DNA Testing for SMA – 1st line

- **SMN gene deletion test (Athena, Quest, Invitae)**
  - Via molecular genetic PCR-based testing (2-3 weeks for result; now quicker)
  - 95% sensitivity, 100% specificity
  - 95% will have homozygous deletions of SMN1
    - 90% homozygous absence of exons 7 and 8
    - 10% show homozygous absence of exon 7 but not 8
  - ~4% of SMA patients exhibit intragenic **SMN1** mutations instead of deletion

- **EMG** → less used as first line; possibly more in later onset cases

- **Prenatal diagnosis:**
  - Carrier testing/screening in expectant mother
  - Via CVS (10-12\(^{th}\) week GA) or Amniocentesis (14-16\(^{th}\) week GA)
Spinal Muscular Atrophy: Updates in Management
History

Kolb S. Arch Neurol. 2011
Management – Supportive Care

• First line:
  – Clinicians can improve survival by optimal management of respiratory, nutritional, orthopedic health
  – Even in era of new drugs available

• This has dramatically improved since 2007 standard of care document by Wang et al.

• Referral for care to a specialized neuromuscular clinical program (Muscular Dystrophy Association/MDA Clinical Program)
Drug Development
Elevate endogenous FL-SMN protein levels generated by SMN2

Transcriptional SMN2 activation via gene promotor

Restore correct splicing of SMN2 pre-mRNA

Translational activation and stabilization of the FL-SMN protein

Suppression of the SMN2 stop codon to elongate SMN2Δ7 protein

**Therapeutic Approaches**

HDAC inhibitors – Na butyrate, Valproic Acid, 4-phenylbutyrate, SAHA, M344

Regulating DNA methylation of SMN2 gene promotor – VPA, 5-Aza-2’deoxycytidine

Others: interferon, hydroxyurea, indoprofen

HDAC inhibitors

Small antisense RNA molecules → Nusinersen

Other – aclarubicin, Na vanadate

Phosphatases and kinases

SMA modifying factors - albuterol

Aminoglycosides

**Gene Replacement**

Improve Motor Neuron Viability

Neurotrophic factors - cardiotrophin

Neuroprotective compounds - Riluzole

Regular exercise
Drug Development Pipeline

<table>
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<th>BASIC RESEARCH SEED IDEAS</th>
<th>PRECLINICAL: DISCOVERY</th>
<th>CLINICAL DEVELOPMENT</th>
<th>FDA APPROVAL</th>
<th>TO PATIENTS</th>
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<tr>
<td></td>
<td>IDENTIFICATION</td>
<td>OPTIMIZATION</td>
<td>SAFETY &amp; MANUFACTURING</td>
<td>PHASE 1</td>
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<td>Columbia/NU-p38a/MDAPK Inhibitor</td>
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<td>Imago-JNK Inhibitor</td>
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Clinical Trials

- **Olesoxime**: Cholesterol-oxime: NCT02628743
  - Targets mitochondrial integrity in stressed cells \(\rightarrow\) promote motor neuron survival
  - Safe and well tolerated – 2 year study
    - 160 patients with Type 2 and nonambulant Type 3 ages 3-25 yrs
    - Primary endpoint not met, secondary endpoint suggests this may maintain motor function in patients with Type 2 or Type 3 SMA over 24 month period

- **Roche/ PTC: RG7800/** –
  - Selectively modulates inclusion of SMN2 exon 7 \(\rightarrow\) orally bioavailable
  - Phase I – safe in HV
  - Phase Ib/Ila – randomized placebo control trial in adults and pediatric SMA patients \(\rightarrow\) suspended due to unexpected eye condition
  - Modified compound: **RG7916/ R07034067** \(\rightarrow\)
    - Phase I/II studies in infants with:
      - Type 1 SMA (NCT02913482)
      - Type 2 and Type 3 SMA patients (NCT02908685)
Clinical Trials

- **Cytokinetics/Astellas**: CK-107/CK-2127107: NCT 02644668
  - Skeletal muscle troponin activator $\rightarrow$ slow calcium release $\rightarrow$ increased skeletal muscle contractility $\rightarrow$ enhance performance
  - Completed Phase I study in HV
  - In Phase 2 – DB/PC/ multi-dose study in patients with Types 2,3 and 4 SMA

- **Avexis: Gene Replacement**: AVXS101 (AAV9)
  - Strong preclinical data in mice (improved motor function, survival, weight, gene expression)
  - Strong phase I clinical data: Type 1 SMA (2 copies SMN2)
    - Mean age treatment 6.3 months

**Outcomes:**
- 11 sat unassisted
- 9 rolled over
- 11 fed orally and could speak
- 2 walked independently
Clinical Trials: Gene Replacement: Enrolling

• Pre-Symptomatic Study of Intravenous AVXS-101 in Spinal Muscular Atrophy (SMA) for Patients With Multiple Copies of SMN2 (SPR1NT): NCT03505099
  – Pre-symptomatic Type 1, 2 or 3 SMA (2,3 or 4 copies SMN2); intravenous
• Study of Intrathecal Administration of AVXS-101 for Spinal Muscular Atrophy (STRONG): NCT03381729
  – Type 2 SMA (3 copies SMN2); intrathecal
• Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 (STR1VE): NCT03306277
  – Type 1 SMA (2 copies SMN2); intravenous

A rapidly evolving space for research and therapeutic development...
Approved Therapeutics
Antisense Oligonucleotide (‘ASO’)
(Nusinersen – Biogen/ Ionis)

• Goal – Manipulate RNA sequences to increase exon-7 incorporation during SMN2 RNA processing → therefore increase FL-SMN

• Need drug that can have effect within the CNS

• ASO’s do not cross BBB

• With IT delivery – can get ASO’s distributed into neurons, microglial cells, and astrocytes
Trials

• Double blind controlled clinical trial in 121 patients with SMA type 1 dosed < 7 months of age:
  – IT administration
  – Analysis in 82 patients showed motor improvement in 40% of patients on treatment vs none in sham group
  – Trial halted, all patients rolled into open label extension

• Study in presymptomatic patients with 2 or 3 copies of SMN2 showed favorable results

• FDA approval December 2016
Spinraza ® (nusinersen)

- Antisense oligonucleotide
- Modifies the transcription of SMN2 to produce a full-length SMN protein.
- Only effective for SMA caused by deletions/ point mutations of SMN1
- Approved for use in patients of all ages with 5q SMA
- Given via intrathecal injection, 12 mg (in 5 mL solution) – single dose vial
- Induction phase, then maintenance every 4 months for life
Treatment

• Genetic Testing
• Baseline evaluation with laboratory testing
• Clinical documentation and consent for treatment/financial review
• Payer authorization
• White bag process for drug acquisition
• Scheduling (!)
• Loading doses
  • Weeks 1,3,5,9
  • Safety labs
  • Biobanking
• Multidisciplinary f/u
• Maintenance dosing every 4 months
Spinraza ® (nusinersen) at Children’s National

- 32 patients on drug (8 Type 1, 10 Type 2, 14 Type 3 SMA patients)
- 28 in maintenance, 3 in loading, 1 awaiting first loading dose
- 1 international patient
- One of largest injecting sites in region (total 164 injections)
- One of earliest sites to initiate clinical dosing of Spinraza in 3/2017
- Tracking motor function, respiratory function, speech/communication, and biomarkers
- All patients showing subjective and objective functional gains; better tolerance to respiratory infections; increased energy; improved motor milestones
- 1 prenatally diagnosed patient → prenatal referral → baby seen immediately postnatally, predicted type 2 or type 3 SMA → Dosed by 5 weeks of life
Cure SMA Center Designation - 2018

Children’s Clinical Core:

- Advanced Practitioners
- NM Neurologist
- Physiatry
- Pulmonology
- Physical Therapy
- Speech Pathology
- Cardiology
- Nutrition
- Interventional Radiology
- Intensive Care
- Lab (Biobanking)
- Anesthesiology
- Financial Specialist
- Pharmacy
- Genetic Counselor
- Palliative Care Team
- Social Work

Patient ↔ Coordinator
Patient Management

• Medical treatment: Spinraza
• Nutrition: swallow, feeding, fluids, calories
• Respiratory: adequate ventilation and pulmonary toilet
• Communication: dysarthria, phonation, devices
• Self Care: occupational therapy, adaptive equipment
• Mobility: physical therapy, mobility devices +/- power
• Positioning: joint integrity, scoliosis
When to Treat?

• Based on electrodiagnostic studies in pre-symptomatic patients (Finkel R. 2012, Swaboda K. 2005):
  – Early preservation of the motor unit
  – Precipitous drop
  – Then more gradual decline

• There may be a critical window for treatment based upon natural history and timing of motor neuron loss
  – This is further reinforced by trial data
  – EARLIER IS BETTER!!!

- Benchmark for prenatally/ NBS neonatally identified cases:
  - Predicted Type 1 SMA: Dose within 3-4 weeks of life
  - Predicted Type 2 or Type 3 SMA: Dose within 2 months of life
Take Home Points

• When to suspect SMA?.... Weakness, hypotonia, areflexia, tongue fasciculations, fine tremor (on reaching), relative facial sparing

• What to do?...... Referral to neuromuscular specialist

  Children’s National Health System:
  Neuromuscular Coordinator:
  Kathleen Smart:  202-476-6193
  ksmart@childrensnational.org

• Counseling/ information?.... www.curesma.org

• When to treat?.... Earlier is better!!
Thanks!

- **ksmart@childrensnational.org**  ***1st contact****
  – Neuromuscular/ MDA/ Cure SMA coordinator

- **dbharuch@childrensnational.org**
  – Neuromuscular Neurology, Co-director Cure SMA Center

- **shevans@childrensnational.org**
  – Chief, Physical Medicine & Rehabilitation, Co-director Cure SMA Center
References

• Bosboom WMJ, Vrancken AFJE, van den Berg LH, Wokke JHJ, Iannaccone ST. Drug treatment for spinal muscular atrophy types II and III. The Cochrane Collaboration. 2009 and 2012.


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