SMA Clinical or Classification & Clinical Features of the Spinal Muscular Atrophies

John T. Kissel, M.D.
Professor of Neurology, Pediatrics & Neuroscience
Wellstone/NCH/OSUMC Myology Course
August 27, 2015

THE OSU MEDICAL CENTER
Disclosures

- Consultant for ISIS for clinical trial in DM1
- Consultant for Cytokinetics for FSHD, SMA studies
- Received support for MG study from Alexion
- Will be (sort of) discussing some off label uses of drugs and agents

- Will *not* be giving a comprehensive overview of *every* type of SMA
Classification of SMA
Objectives

- Overview of terminology and classification scheme related to the SMA group of diseases
- Review clinical features of most common SMAs
  - Proximal SMA, esp. 5q SMN-related SMA
  - Touch on variants, special features
- Laundry list of several less common SMAs
- Outline a reasonable conceptual approach to these patients
Spinal Muscular Atrophy
Who Cares?

- More common than most realize; affects all ages
  - Most common fatal genetic disease of infants
  - 1 in 11,000 births (Sugarman et al, EJHG 2012)
  - Overall carrier frequency ~1:54 (>72,400 specimens)
  - 1:35 (Prior, 2010) to 1:72 for Af. Am. (Sugarman, 2012)

- Unique genetics - typifies “translational research”
  - Appeals to molecular geneticists!
  - Leading directly to clinical trials
  - It’s a “cool” disease to study!!

- “Hot” at NIH - 1st NIH NeuroNEXT (Kolb; OSUWMC)
  - ~15 biotech companies developing therapies
37 y.o. police officer with
- 1 yr trouble with stairs
- 10 yrs of ? leg weakness
  - Difficulty shooting
- Muscle twitches/cramps
- FHx negative (4 brothers)
- Exam: 2-3 HF, HE; 4- KE, KF; otherwise solid 5s!
- UEs, sensation, ref. normal
- EMG - “diffuse denervation”
  - Dx of ALS made
Spinal Muscular Atrophy
Case Presentation

- SMN gene analysis - Homozygous deletion SMN 1 exons 7 & 8
  - 5 copies SMN 2

- Diagnosis: Not ALS
  - 5q SMA
“Spinal Muscular Atrophy”
Terminology

- **Group** of diseases affecting lower motor neurons
- Most commonly (but not exclusively) **genetic**
  - May involve numerous different genes
  - By far most common is 5q11-13 gene
  - Named by inheritance type, area involved
- Less commonly (formerly) an **acquired** disorder
  - Early phase of ALS (before UMN sx appear)
  - Progressive muscular atrophy (PMA)
### Distal SMA (HMN) Genetic Classification

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### Autosomal recessive

| SMARD1 (HMN6) | 11q13 | IGHMBP2 |
| Distal SMA 3 | 11q13.3 | ?       |
| HMNJ (Jerash) type | 9p21.1-p12 | ?       |
| Distal SMA 4 | 1p36 | PLEKKG5  |
| Distal HMN@ | 7q11 | HSP27    |

- Only a partial list!
- Allelic to: *CMT 2L; **CMT 2D; *** Silver syndrome; @ CMT 2F
# Proximal SMA

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<td>?</td>
<td>?</td>
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* same locus as distal HMN2
+ other loci identified
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<td>SMA 1-4 (SMN protein-related)</td>
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<td>SMN</td>
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<td>5q13</td>
<td>SMN</td>
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<td>SMA 2</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>SMA with congenital fractures</td>
<td>?</td>
<td>?</td>
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<tr>
<td>SMA with pontocerebellar hypoplasia</td>
<td>14q32</td>
<td>VRK1</td>
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<tr>
<td>Most SMA IV</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Werdnig; Hoffman</td>
<td>1891,1892</td>
<td>Initial descriptions; pathology</td>
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<tr>
<td>Byers and Banker</td>
<td>1961</td>
<td>3 functional groups proposed</td>
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<td>Dubowitz</td>
<td>1964</td>
<td>Milder disease if onset &gt; 6 mos.</td>
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<td>Kugelberg, Welander</td>
<td>1966</td>
<td>Onset 2-17 yrs; adult survival</td>
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<td>Munsat/MDA</td>
<td>1991</td>
<td>3 type classification formalized</td>
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<tr>
<td>Russman et al</td>
<td>1992</td>
<td>New thoughts on classification</td>
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SMA Type 1
Acute Werdnig-Hoffman

- Dec. fetal movement
- Onset < 6 mos.
- Hypotonia, weakness; legs > arms; never sit!
  - Poor head control
- Bulbar muscle weakness
  - Weak suck, swallow
- Tongue fascics in 50%
- Reflexes absent
- Bell-shaped chest
- Respiratory distress
  - Death < 2 years (70%)
SMA Type 2
Late Infantile; Chronic W-H

- Normal to 6 - 8 months; onset < 18 mos
- Poor rollover & crawl
- Weak sitting (tripod)
- Legs weaker than arms
- Never achieve ability to stand!
- Reflexes absent in 70%
- Contractures, scoliosis
- Much longer survival
SMA Type 3
Childhood SMA; Kugelberg-Welander

- Onset usually 2-12 y.o.
- Usually presents with difficulty in walking
  - Waddling gait; lumber lordosis; stair troubles
- Gower's maneuver
- Legs weaker than arms
- Fasciculation florid
- Reflexes dec-absent
- Often normal survival
SMA Type 4
Adult SMA

- < 5% of all 5q SMA
  - ~ 0.32 per 100,000
- Onset >age 18-21
- Slowly progressive limb girdle weakness
- Fasciculation's in 75%
  - Mistaken for ALS
- “Benign” prognosis with normal survival
SMA 3b
SMA Type 0
Fatal Neonatal

- McLeod et al, 1999
  - Five patients
- Decreased fetal movement
- Neonatal hypotonia
- Early resp. failure
- Death without ventilator support
- Rudnik-Schoneborn et al, 2008
  - ? ASD, VSD

Photo courtesy of K. Swoboda
## SMA Classification
### Updated 1991 Clinical Criteria

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<tr>
<th>Type</th>
<th>Onset</th>
<th>Function</th>
<th>Death</th>
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<tbody>
<tr>
<td>0</td>
<td>Prenatal</td>
<td>Resp support</td>
<td>Neonatal</td>
</tr>
<tr>
<td>1</td>
<td>0 - 6 mos.</td>
<td>Never sit</td>
<td>&lt; 2 yrs.</td>
</tr>
<tr>
<td>2</td>
<td>&lt; 18 mos.</td>
<td>Never stand</td>
<td>&gt;2 yrs.</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 18 mos.</td>
<td>Stand alone</td>
<td>Adult</td>
</tr>
<tr>
<td>3a</td>
<td>&lt; 3 years</td>
<td>Stand alone</td>
<td>Adult</td>
</tr>
<tr>
<td>3b</td>
<td>&gt; 3 years</td>
<td>Stand alone</td>
<td>Adult</td>
</tr>
<tr>
<td>4</td>
<td>&gt;21 years</td>
<td>Stand alone</td>
<td>Adult</td>
</tr>
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</table>
CureSMA Data Base

- FSMA data on newly diagnosed families
- Over 3 years data currently
  - Annually, ~400 newly diagnosed patients in the US contact FSMA:
    - 50% Type 1
    - 25% Type 2
    - 10% Type 3
    - 7% Type 4
    - 8% Unknown
- Capturing 60-90% of new pt. population!

Zerres et al, 1995
N=445

Courtesy Jill Jarecki, FSMA 2012
Tremendous variability between types
  - Both within and between families
    - e.g. Strong vs weak sitter
  - Dubowitz’s scheme of 2.1 – 2.9

As many as 1/3 patients don’t fit “cleanly” in the scheme (e.g. onset < 18 mos. but stand)
  - Function is better predictor of prognosis and better for typing than age of onset
# Prognosis of SMA

*Zerres et al; 1995, 1997*

<table>
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<tr>
<th>Type</th>
<th>Ambulatory at 10 Yrs.</th>
<th>Ambulatory at 40 Yrs.</th>
<th>Alive at 5 Yrs.</th>
<th>Alive at 25 Yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 (n=197)</td>
<td>NA</td>
<td>NA</td>
<td>~7%</td>
<td>0%</td>
</tr>
<tr>
<td>Type 2 (n=240)</td>
<td>NA</td>
<td>NA</td>
<td>98.5%</td>
<td>68.5%</td>
</tr>
<tr>
<td>Type 3A (n=195)</td>
<td>70.3%</td>
<td>22%</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td>Type 3B (n=134)</td>
<td>96.7%</td>
<td>58.7%</td>
<td>100%</td>
<td>97%</td>
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</table>
Spinal Muscular Atrophy

A Timely Review

Stephen J. Kolb, MD, PhD; John T. Kissel, MD

Archives of Neurology
2011 Aug;68(8):979-84
Gene Defect in SMA

Identification and Characterization of a Spinal Muscular Atrophy–Determining Gene

Lefebvre et al, Cell 1995

- Homozygous deletion in the 5q Survival of motor neuron (SMN) gene in ~95% of SMA (all 3 types!)
- Simplified the diagnosis - - no muscle biopsy needed for diagnosis; ? even if EMG needed!
- Led to development of animal models
- Launched investigations on the molecular pathogenesis
- Led (eventually) to explanation of phenotypic variability
SMN 5q Gene Region Structure

Inverted-Duplicated Gene

Position 840 C to T base Δ-disrupts ESE; creates ESS

Full length mRNA

Truncated mRNA (90%)
SMN Gene Region

Results

- No SMN1 in SMA pts.
- 1 or more copies SMN2
- 90% SMN2 lacks exon 7
- Truncated, unstable, rapidly degraded, low level protein
  
  **BUT**

- 10% is full length SMN
- *Partially* compensates
- Phenotype variability relates to SMN2 copy #

*Butchbach, 2008*
SMA Phenotypes
SMN 2 Copies

N = 52 SMA 1 and 90 SMA 3 patients

Mailman MD et al; 2002; Prior Lab
# SMA Updated Classification

**Type** | **Onset**  | **Function** | **Death** | **SMN2 #**  
---|---|---|---|---
0 | Prenatal | Resp support | <1 mo. | 1 
1 | 0 - 6 mos. | Never sit | <2 yrs. | 2 
2 | < 18 mos. | Never stand | >2 yrs. | 3, 4 
3 | > 18 mos. | Stand alone | Adult | 
3a | < 3 years | Stand alone | Adult | 3, 4 
3b | > 3 years | Stand alone | Adult | 4 
4 | >21 years | Stand alone | Adult | 4-8 

Molecular genetics validated the clinical classification!!
45 SMA adults stratified by SMN2 copy # (3 vs 4)

- 3 copy pts. - earlier onset; worse SMA-FRS (p=0.02)
  - Less likely to be walking (31% vs 70%; p=0.009)

- SMN2 # is main determinant of disease severity!
Non-SMN2 Phenotypic Modifiers
Prior et al, AJHG 2009

A Positive Modifier of Spinal Muscular Atrophy in the SMN2 Gene

Thomas W. Prior, Adrian R. Krainer, Yimin Hua, Kathryn J. Swoboda, Pamela C. Snyder, Scott J. Bridgeman, Arthur H.M. Burghes, and John T. Kissel

• 3 pts (age 29-41) —mild 3b phenotype; 2 copies SMN2
• Exon 7 c859 G>C mutation that created ESE element
  ➢ Increased full length SMN transcript & protein
• Not all SMN2 is created equal!
• Other modifiers identified and expected!
• Can’t always deduce phenotype from genotype!
• Nature may be telling us how to treat this disease!
Smn (SMN1) deletion lethal in mice

- Mice have no SMN2
- 2 copies SMN2 yields SMA mice
- More SMN2 - milder phenotype
- 8 copies SMN2 rescues mice

Imp. for studies on pathogenesis, drug screening (11 models & PIG!)
SMN Function
Unresolved Issues

- Why are motor neurons more affected than other neurons or other cells?
  - Do MNs need more SMN?
  - Is SMN more reduced in motor neurons?
  - Does SMN have other functions in motor nerves?

- What downstream pathways/mRNAs are affected?
  - StaSiMoN (stymied in SMA) Pellizoni, 2010

- How much reduction is needed to cause SMA?
  - ~15-20% SMN levels rescue mice (DiDonato)
  - Even a little boost can help a lot!
**Hypothesis:** If low SMN causes MN loss & inc. SMN2 is protective

- Inc. SMN2 expression
- OR
- Converting SMN2 to SMN1
  --Promote exon 7 inclusion
- OR
- Replacing SMN1 gene

Drugs to promote exon 7 inclusion, stabilize SMN2 inc. SMN2 product

Antisense oligonucleotides

Viral mediated gene Transfer (Kaspar et al, 2010)

may “rescue” MNs, prevent MN loss, allow reinnervation
SNM1 gene mutation → SMN1 gene replacement

Retained SNM2 copies → SMN2 activation

Alternative splicing of SNM2 transcripts → Promote exon 7 inclusion

Decreased full-length SMN → Stabilize SMN protein

SMN protein deficiency → Neuroprotection; stem cells

Motor neuron loss → Anabolic therapy

Muscle weakness, atrophy → Supportive care

SMA clinical manifestations

After Sumner, J Child Neurol 2007
Strategies

- SMN1 gene replacement
- SMN2 activation
- Promote exon 7 inclusion
- Stabilize SMN protein
- Neuroprotection
- Stem cells
- Anabolic therapy
- Supportive care

Trials

- AAV trials in development
- Drug trials (albuterol, PBA, VPA, HU); quinazoline
- ASO/small molecule trials
- Indoprofen, proteasome inhibitors, polyphenols
- Gabapentin, riluzole, olesesoxime; stem cells
- Albuterol trials
- Respiratory, orthopedic trials

After Mercuri, Bertini, Iannaccone, Lancet Neurology 2012
**PC-SMA Clinical Trials**
Swoboda et al; 2010, 2011; Kissel et al 2012

- **CARNIVAL 1**: 1 yr. PRDBPCT of 60 SMA “sitters” 2–8 yrs.
  - Crossover design after 6 mos.; MHFMS-Extend
  - No sig. difference between groups except in children < 3 years treated for 1 year (p=0.030)

- **CARNIVAL 2**: 1 yr open in 30 “walkers” 3-17 years
  - No effect; except inc. CMAP amplitude at 6, 12 mos.

- **VALIANT**: PRDBPCT 30 walking adults (age 18-60)
  - Crossover design after six months
  - NO change in ANY outcome parameter (M&N 2013)

- Open label infant study in 39 type 1’s; data presented 6-12-12; no change in natural history.
Clinical Protocol
Mendell et al, 2014

- Single-site, Phase I gene transfer trial in SMA type 1
- N = 9 clinically affected subjects, <9 mo of age, proven SMN1 mutation (bi-allelic) with 2 copies of SMN2
- scAAV.CB.SMN will be delivered intravenously
  - Cohort 1 (Low Dose) 6.7 X 10^{13} vg/kg (n=3)
  - Cohort 2 (High Dose) 3.3 X 10^{14} vg/kg (n=6)
- Primary Outcome measure: Safety
- Secondary outcome measures:
  - Time to ≥ 16-hour resp. assist/day or death
  - Efficacy: 50% subjects alive/ventilator free at 2 yrs
  - But ? natural history
SMA Biomarkers in the Immediate Postnatal Period of Development

Steve Kolb (PI): “To identify prognostic and surrogate biomarkers of dx. progression to facilitate clinical trials.”

15 NeuroNEXT Centers to recruit 27 Type 1 infants; 27 age-matched controls < 6 mos. (? Pre-symptomatic)

Prospective longitudinal, natural hx study (Sept, 2012)

Evaluations at 0, 3, 6, 9, 12, 18, 24 months

- Physiologic biomarkers – EIM and CMAP
- Functional biomarkers – TIMPSI and CHOP-Intend
- Molecular biomarkers – mRNA; protein; BforSMA analyte panel

27 normals and 26 SMA enrolled as of 9/2014! (12 deaths)
SMA 5q Variants
SMN Related

- Resp. distress at birth, death w.o. ventilation
  - McLeod et al, 1999; five patients (type 0)
- Arthrogryposis multiplex congenita
  - Burglen et al, 1996; six patients (out of 12)
- Facial diplegia and external ophthalmoplegia
  - Korinthenberg et al, 1997; three patients
- Cong HD (ASD or VSD) in 75% with 1 SMN2
  - Rudnik-Schoneborn et al, 2008; four pts.

Consider SMN assay in atypical SMA cases!
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X-linked Bulbo-Spinal Atrophy
Kennedy’s Disease

- Onset 15-60 yrs
- Hand tremor & proximal leg symmetric weakness
  - Atsuta et al, 2006; n=223
- Mouth, tongue atrophy, weakness, fasciculations
- Sensory loss in feet, legs
- Gynecomastia
- CAG repeat in XLR-Xq12 androgen receptor gene
  - Genetic test available
Kennedy’s Disease
Lethal X-Linked Infantile SMA
Ramser et al, 2008

- Rare; ~16 families
  - Recruiting more!!
- Congenital hypotonia
- Arthrygropyosis ± fxs
- Myopathic face, dysmorphic, digital contractures
- Respiratory distress, death < 1 year
- Defect in Xp11 UBE1 (ubiquitin-activating enzyme E1)
Distal SMAs
Overview

- Also known as hereditary motor neur(on)opathy (HMN)
- Usually autosomal dominant
  - 13 chromosomal localizations, 7 genes identified
- Usually presents in childhood with anterior tibial & peroneal compartment weakness; occ starts in UEs
  - Weakness spreads proximally, involves arms
  - Spares sensation clinically and by EPS
  - Other features (pyramidal, musculoskeletal) variable
- Overlap with other diseases (especially CMTs, HSPs)
- Uncommon; often only a few pedigrees reported for many types
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<td>Distal SMA 4</td>
<td>1p36</td>
<td>PLEKKG5</td>
</tr>
<tr>
<td>Distal H MN@</td>
<td>7q11</td>
<td>HSP27</td>
</tr>
</tbody>
</table>

- Only a partial list!
- Allelic to: *CMT 2L; **CMT 2D; *** Silver syndrome; @ CMT 2F
SMA with Respiratory Distress
SMARD1; HMN6

- <1% infantile SMA
- Presents < 6 mos.
- Diaph. paralysis; eventration
  - Acute respiratory failure
- Hand and foot weakness & contract paralysis
  - Talipes, fatty finger pads
  - Growth delay
- AR; chromosome 11q13.3
  - IGHMBP2 gene

Kaindl et al, J Child Neurol 2008
**Distal SMA/N/HMN**

**Hearing Loss**

- AD; 10 affected; 3 gens.
- Onset in 1st-2nd decade
- Distal to prox. weakness
  - Sensory sparing
  - Fatty pads!
- EMG in 4; sensory normal
- SN hearing loss - hearing aids
- Linkage analysis in Kolb laboratory
  - Chromosome 19q13
  - ? New region – NOT
  - MYH14 mutation (2011)
Distal SMA with Hearing Loss

Pes planus
Bilat foot drop
SMA Approach

Overview

?SMA? SMN gene analysis

SMN1 del. positive

5q SMA

SMN1 del. negative

EMG-confirm denervation

Proximal SMA Features

SMN 1 count & gene sequencing

+ SMN 1 mutations

No SMN 1 mutations

Atypical Features

Diagnosis ? non-specific.

+ SMARD, dSMA, XL-SMA

Genetic Test Uncommon

Modified from Lunn & Wang Lancet, 2008

SMA Approach Overview

5q SMA

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Consensus Statement for Standard of Care in Spinal Muscular Atrophy

Ching H. Wang, MD, PhD, Richard S. Finkel, MD, Enrico S. Bertini, MD, Mary Schroth, MD, Anita Simonds, MD, Brenda Wong, MD, Annie Aloysius, MRCSLT, HPC, Leslie Morrison, MD, Marion Main, MCSP, MA, Thomas O. Crawford, MD, Anthony Trela, BS, and Participants of the International Conference on SMA Standard of Care

- Use team approach - RN, PT, OT, ST, RT, SW
  - Pulmonary, orthopedics, PM&R, orthotists, psychologists
  - SMA specialty clinics
- Always consider function and QOL issues
- Meticulous pulmonary management (Schroth M, 2009)
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Thank you for your attention….

And a final word for the overworked!
- Early (pre-clinical) diagnosis is crucial to identify patients and best candidates for therapy EARLY!
- 40,103 newborn blood spots from Ohio DH screening lab
- DNA test, Luminex double label technology
- 4 homozygous SMN1 deletions identified & confirmed
  - 2 had 2 SMN2 (Type 1); 2 had 3 SMN2 (Type 2 or 3)
- Controversial in untreatable dx; ACOG did NOT support cost effectiveness; not metabolite assay
- Swoboda NIH funded study for Utah, Colorado
- Mandatory as we move forward with therapy trials