Care of the Child with Spinal Muscular Atrophy

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Spinal Muscular Atrophy: Facts

- Autosomal recessive
- Most common lethal disease in children under the age of 2
- Incidence 1 in 6,000 to 10,000 live births
- No ethnic predisposition
- No gender predisposition

SMA Definitions

- Motor Neuron Disease:
  - Motor neurons act as conductors
  - In SMA motor neurons lack SMN protein
  - Without SMN protein motor neurons weaken
- Neuromuscular disease of the peripheral nervous system
  - Cell body in spinal cord
  - Neuromuscular junction
  - Muscles

Clinical Classification of SMA

<table>
<thead>
<tr>
<th>SMA type</th>
<th>Age of Onset</th>
<th>Highest Function</th>
<th>Natural Age of Death</th>
<th>Typical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>0-6 months</td>
<td>Never sits</td>
<td>2 years or younger</td>
<td>Profound weakness, impaired head control, weak cough, fine hand tremors, respiratory insufficiency</td>
</tr>
<tr>
<td>Type II</td>
<td>7-18 months</td>
<td>Never walks</td>
<td>2 years or older</td>
<td>Delayed motor milestones, poor weight gain, weak cough, fine hand tremors, contractures, scoliosis</td>
</tr>
<tr>
<td>Type III</td>
<td>18 months or older</td>
<td>Stands and walks</td>
<td>Adult</td>
<td>Variable muscle weakness, loss of ability to walk at some point in life</td>
</tr>
</tbody>
</table>

Spinal Muscle Atrophy with Respiratory Distress

- Severe form of SMA type I
- Affects upper spinal cord more than lower
- Different genetically from SMA type I
- IGHMBP2 gene on chromosome 11q13-q21
- Key differentiating feature is the severe respiratory distress

Spinal Muscular Atrophy with Respiratory Distress

Suspect SMA When....
Chromosomes and Genes
- Chromosomes are the unit of genetic transmission
- Genes are individual sections of DNA
- Exons and introns are components of genes

Protein Synthesis

Control of Protein Synthesis

Genetic Mutations
- Mistakes in the DNA sequence
- When copied make defective proteins
- Types
  - Promotor
  - Single nuclotide/single point
  - Deletion
- SMA is a deletion mutation

Survival Motor Neuron (SMN) Genes
- SMN protein required for motor function
- Two nearly identical genes, SMN1 and SMN2

SMN1 vs. SMN2
Each SMN1 copy: 100% of needed SMN protein
Each SMN2 copy: 10% of needed SMN protein
Insufficient SMN protein causes SMA

- Absence of the SMN1 = diagnosis of SMA

SMN2 influence on severity

- Each SMN2 copy: 10% of needed SMN protein
- More severe
- Less severe

- SMN2 copy number influences motor ability
- SMN2 copy number cannot always predict outcome

Autosomal recessive inheritance

- 25% chance unaffected
- 50% chance carrier
- 25% chance affected

Carrier frequency: 1/40 – 1/60

Genetic Testing

- SMA deletion test (SMN1D)
  - Highly diagnostic
  - Detects presence or absence of SMN 1
  - Tells number of copies of SMN 2
  - 95% of patients will be identified by this test
  - Does not detect the 5% who have point mutations on SMN 1

Pulmonary Care & Complications

- SMA affects intercostal and accessory muscles
- Diaphragm spared
- Type of SMA heavily influences pulmonary function

Pulmonary Risk by SMA Type

<table>
<thead>
<tr>
<th>Type/onset of symptoms</th>
<th>Respiratory manifestation</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA type I 6 months or younger</td>
<td>Early onset respiratory insufficiency</td>
<td>1. Supportive care until natural death</td>
</tr>
<tr>
<td></td>
<td>Recurrent pneumonia</td>
<td>2. Noninvasive ventilation (temporary)</td>
</tr>
<tr>
<td></td>
<td>Without support child will die from respiratory compromise or acute pneumonia</td>
<td>3. Tracheostomy and mechanical ventilation (Kielberg)</td>
</tr>
<tr>
<td>SMA type II 18 months or older</td>
<td>Nocturnal hypoventilation</td>
<td>4. Pulmonary clearance</td>
</tr>
<tr>
<td></td>
<td>Progressive respiratory insufficiency</td>
<td>1. Noninvasive ventilation during sleep (can be long term)</td>
</tr>
<tr>
<td></td>
<td>Recurrent pneumonia and atelectasis</td>
<td>2. Tracheostomy and mechanical ventilation (Kielberg)</td>
</tr>
</tbody>
</table>

SMA type III Schoolage years

- Nocturnal hypoventilation

1. Noninvasive ventilation
2. Pulmonary clearance
Pulmonary Assessment-Physical Exam

- Chest configuration
- Presence of pectus
- Work of breathing
- Breath sounds

Radiology-Chest x-ray

Respiratory Measures

- Oxygen Saturation
- Carbon Dioxide
  - End Tidal
  - Transcutaneous
- Blood Gas

Pulmonary Function Testing

- Evaluates respiratory muscle strength
- Important Parameters
  - Forced vital capacity
  - Forced vital capacity time 1
  - Peak cough flow

Polysomnography-Sleep Study

- Diagnostic
- Hypoventilation
- Obstructive sleep apnea
- Sleep disordered breathing

Pulmonary Clearance-Medications

- Bronchodilators-Open airways to promote mucus clearance
  - Short acting beta agonists
  - Long acting beta agonists
  - Short acting anticholinergic
- Inhaled corticosteroids-not typically used unless history of airway reactivity
Pulmonary Clearance-Medications

- Mucolytic-thin secretions for easy removal
  - Hypertonic saline 3% or 7%
  - Dornase Alfa (Pulmozyme)
- Inhaled antibiotics-used in cases of recurrent pulmonary exacerbations by susceptible pathogens
  - Tobramycin (TOBI)
  - Aztreonam (Cayston)

Important Order of treatments

- Bronchodilator
- Mucolytic
- Chest percussion or chest oscillator vest
- Suction
- Inhaled antibiotic
- Inhaled corticosteroid

Pulmonary Clearance Manual

Chest Oscillator Devices

Cough Assist Devices/cofflator/ex-sufflator

Respiratory Support Devices-Bipap

- Noninvasive
- Limited settings
  - Inspiratory pressure
  - Expiratory pressure
  - Respiratory rate
- Most are downloadable
Respiratory Support Devices-Trilogy

• Approved for both invasive and noninvasive support
• Multiple modes
  – AVAPS
  – PC
  – PS
• Downloadable
• Portable-6 hour battery

Respiratory Support-Laptop Ventilator

• Primarily for invasive ventilation
• Modes
  – Pressure/volume
  – AC/SIMV/PS
• External battery required
• Not downloadable

Noninvasive ventilation-interfaces

Compliance with NIPPV

• Difficult for kids to acclimate to support
• Many fears
• Strategies to improve compliance
  – Starting with short wearing time
  – Positive reinforcement
  – Frequent contact with health care providers

Importance of a Respiratory Sick Plan

• Acute illness is not planned! Families need to be prepared.
• Components:
  – Bronchodilation
  – Pulmonary clearance
  – Management of pain/fever
  – Defined emergency contact for advice
  – Defined emergency center for care

Nutrition and Gastrointestinal Issues

• Children with SMA are at risk for:
  – Dysphagia and aspiration
  – Slow gut motility
  – GERD
  – Abdominal pain, bloating and gas
  – Ileus especially during acute illness
  – Constipation
  – Low muscle mass effects metabolism
  – Hyper/hypoglycemia
  – Abnormal fatty acid metabolism


Nutritional Assessment

- Growth including height/weight
- Labs
  - Electrolytes
  - Vitamin D
  - Fatty acid profile
  - Glucose
- Intake assessment/food diary
- Schedule
- Results of video fluoroscopic swallow study

Nutritional Management

- Nutrition best assessed and managed by a registered dietician familiar with SMA care.
- Very controversial with strong opinions
- Very limited well conducted clinical or bench research

Nutritional Management

- Oral feeders
  - Well balanced diet
  - Appropriate fluid intake
  - Supplements only as indicated by labs
- Tube feeders-options
  - Blenderized diet
  - Commercial formulas
  - Supplements

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Nutritional Guidelines:

- Calories: reduced lean body mass so
  - range from 7 - 11 calories per cm height as a typical daily requirement
- Fluids: Typical maintenance daily fluid requirements are 115 - 135 ml per kg body weight
- Protein: 1.0 - 2.0 grams/kg/day total
- Fat: 15-20% of total calories

Personal communications: General nutritional guidelines for SMA Children from Kathryn Swoboda MD and Rebecca Hurst RD 2010

Special Nutritional Situations

- Pre-Operative Fasting
  - In general not recommended to fast for more than 6 hours
  - For longer pre-operative fasting may need IV nutrition
- Acute Gastroenteritis
  - Poor toleration of glucose and electrolyte imbalances
  - For prolonged illness seek emergency care for IV fluids and nutrition

Nutritional Risk Factors: Fasting

- Muscle acts a “buffer” or source of carbs, protein and fat during fasting
- Low muscle mass limits the buffering ability
- Liver can supply glucagon which can sustain blood glucose for 6-8 hours into fasting
- Afterward muscle becomes source of glucose
- Hypoglycemia is a signal for muscle breakdown in the absence of food
- Children with SMA I have case reports of abnormal fatty acid metabolism-which is a source of glucose during fasting
- This is why children with SMA can not tolerate prolonged periods of fasting.


Managing Constipation

- Nutritional options for prevention
  - High fiber diet
  - Prune juice
  - Fluid goals
  - Blenderized diet
- Bowel program
  - Scheduled toilet time daily
  - Medications

Medications for Constipation

- Laxatives
  - Osmotic agents
  - Bulk formers
  - Stool Softeners
  - Stimulants
- Enema/rectal agents
  - Glycerin suppository
  - Saline enema
  - Stimulant
- Plan for acute event
  - Suppository
  - Osmotic agents

Management of GERD

- Preventive care
  - Positioning
  - Thickening feeds
- Medications:
  - Proton pump inhibitors-first line
    - Not available as a liquid
    - Dose 1-2mg/kg/day
    - 30 minutes before meals
  - H2 receptor inhibitors-second line
    - Dose 0.1mg/kg/dose 2-3 times daily divided BID
- Motility agents:
  - Metoclopramide
    - 0.1mg/kg/dose 2-3 times daily
  - Erythromycin
    - 1-3mg TID
  - Proton pump inhibitors-first line
    - 1-2mg/kg/day divided BID
    - 30 minutes before meals
  - H2 receptor inhibitors-second line
    - 8-10mg/kg/day divided BID
  - Motility agents
    - Metoclopramide
      - 0.1mg/kg/dose 2-3 times daily
    - Erythromycin
      - 1-3mg TID
  - Metformin

Management of Abdominal Pain and Bloating

- SMA type II heavily affected
- No well established treatments
- Nutrition
  - Avoid slow digesting/gas forming foods
  - Consider elemental formula
  - Small frequent meals
  - Fluids
  - Upright position when eating
- Gastrostomy tube
  - Chimney
  - Venting
  - Farrel bag
- Ileus
  - At risk for development
  - During acute illness
  - Needs inpatient care
  - NPO, IV fluids

Orthopedics: Contractures

- Shortening of muscles, tendons and other support tissue
- Occurs secondary to nonuse/weakness
- Prevention:
  - PT/ROM exercises
  - Bracing
- Treatment-Surgical release

Orthopedic Issues: Scoliosis

- Curvature of the spine secondary to weak core muscles
- Associated with:
  - Thoracic restriction
  - Pain
  - Worsening reflux
- Treatment
  - Bracing-TLSO
  - Surgical correction strongly encouraged
    - Young children-growing rods
    - Older children-spinal fusion
Scoliosis Repair-Growing Rods

Orthopedics: Hip Subluxation

• Common in non-walkers
• Acetabulum does not form due to non-weight bearing
• Femoral head slips out of acetabulum
• Treatment
  – Seating systems
  – Physical Therapy
  – Observation
  – Rarely surgery

Orthopedics: Osteopenia

• Bone density is developed and maintained by weight bearing
• Non-weight bearing results in osteopenia
• High risk for fracture
• Treatment
  – Vitamin D
  – Bisphosphonate
  – Handle with care

Neurologic Management-Medications

• Oral albuterol
  – Dose 2mg QID
  – Limited evidence of efficacy
  – Treated in children with SMA type 2-3 (N=13)
  – Measured changes in FVC, grip strength and DTXA scan
  – Found statically significant improvement in FVC and grip strength
  – Side effects
    – Tachycardia
    – Tremor
    – Worsening contracture
  – Contraindicated for any research study participants

Neurologic Management-Medications

• Depakote-anticonvulsant
  – Evidence-phase 2 clinical trials in children with SMA type 2-3 (N=42)
  – Measured:
    • functional motor scale
    • EMG
    • Blood SMN RNA levels
    • Bone density via DEXA scan
  – No difference between treatment and placebo groups
  – Treatment group had significant weight gain and several subjects lost function secondary to weight gain.

Palliative Care

• May be involved in goals of care discussion for children with SMA type I
  – Opinions vary wildly on recommendations for treatment vs supportive care
  – Physicists in US, pulmonologists, and those with experience in caring for children with SMA more likely to recommend treatment
  – Should be involved early on for long term assistance with goals of care, pain and symptom management


Pain Management

- Adolescents with SMA type II score higher in pain scores than adolescents with Duchene Muscular dystrophy.
- Pain associated with:
  - Scoliosis
  - Hip subluxation
  - Contractures
  - GI pain
- Treatments:
  - Current trends: medications, opioids.
  - Disadvantages:
    - Tolerance
    - Escalating dose needs
- Alternative treatments:
  - Prevention of contractures
  - Medication
  - Botox
  - Seating systems
  - Hospital beds.

IONS-SMN-RX Restoring function on SMN2

Use medication to block splice factors

- Target genetic defect by helping SMN2 to incorporate exon 7.
- Current clinical trials: ISIS-SMNrx.

AveXis-AVXS-101

- One time intravenous infusion
- Gene therapy that carries a functional copy of human SMN gene via an adenovirus capsid shell.
- Crosses blood brain barrier
- Targets motor neurons
- Continuous promoter activates transgene and allows for sustained SMN expression
- Phase one clinical trial has completed enrollment
- Results pending

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