518.89 Neuromuscular Disease with Pulmonary Disease

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Spinal Muscular Atrophy

- Hereditary symmetric muscular atrophy and weakness due to degeneration of the anterior horn cells of the spinal cord and bulbar motor nuclei in some cases
- Most frequent fatal autosomal disorder in infancy 1 in 6,000-10,000 infants

- **SMA Type 1** (Werdnig-Hoffman): Never sits without support, onset in utero to 6 months; autosomal recessive; lifespan 2 years or less
- **SMA Type 2**: Never walks, onset <18 months; lifespan 70% alive at 25 years
- **SMA Type 3** (Kugelberg-Welander): can stand and walk alone, onset >18 months; lifespan normal
## SMA Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Function</th>
<th>Death</th>
<th>SMN2 copy #</th>
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<td>0</td>
<td>Prenatal</td>
<td>Resp support</td>
<td>&lt;1 mo.</td>
<td>0</td>
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<tr>
<td>1</td>
<td>0 - 6 mos.</td>
<td>Never sit</td>
<td>&lt;2 yrs.</td>
<td>1</td>
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<tr>
<td>2</td>
<td>&lt; 18 mos.</td>
<td>Never stand</td>
<td>&gt;2 yrs.</td>
<td>3-4</td>
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<td>&gt; 18 mos.</td>
<td>Stand alone</td>
<td>Adult</td>
<td>3-4</td>
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<tr>
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<td>&lt; 3 years</td>
<td>Stand alone</td>
<td>Adult</td>
<td>3-4</td>
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<td>&gt; 3 years</td>
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<td>Adult</td>
<td>4</td>
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<td>&gt;21 years</td>
<td>Stand alone</td>
<td>Adult</td>
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Spinal Muscular Atrophy

Genetics:

• Loci for all 3 childhood SMA were mapped to chromosome 5q13
• Survival motor neuron gene SMN1 on chromosome 5q13 is SMA determining gene
• 95-98% SMA lack exon 7 in both copies of SMN1;
• 2-5% compound heterozygote for deletion of exon 7 of SMN1 and an intragenic mutation of SMN1
SMA Pulmonary Natural History

**Natural History**

- Normal breathing
- Respiratory and bulbar muscle weakness
  - REM related sleep disordered breathing
  - Ineffective cough reduced peak cough flows
  - NREM and REM sleep disordered breathing
  - Swallow dysfunction
  - Chest infections
  - Daytime ventilatory failure

**Assessment**

- Physical examination
- Pulmonary function, peak cough flow, respiratory muscle strength
- Chest xray, Sleep study
- Swallow function evaluation

**Intervention**

- Airway clearance with cough assistance
- Nocturnal non-invasive ventilation
- Nocturnal or continuous non-invasive ventilation

6 month old SMA type 1
Chest Wall Changes

Normal
Normal

SMA I
SMA II
OMG: What to do?
Pre-Clinical Data: Gene Therapy

• SMA mouse model (SMN2+/+;Smn-/-SMND7+/+)
  - contains 2 copies of SMN2 lacks mouse SMN and developed at OSU in Burghes Lab (Δ7 SMA mouse)

• Develops phenotype of SMA
  – Normal at birth followed by rapid onset and progression with death at 13-16 days (CMAP decline occurs as well)

• IV scAAV9.CB.SMN extends survival to 1 year in P1 mice receiving 3.3 X 10^{14} vg/kg in facial vein (Foust et al 2010)
Congenital Myotonic Dystrophy

- Exhibited at birth with severe generalized weakness or in adolescence with slowly progressive facial and distal extremity weakness and myotonia
- Adolescent form is classic illness associated with arrhythmias, cataracts, male pattern baldness and hypogonadism
- Facial appearance characterized by hollowing of muscles around temples, jaw and neck, ptosis, facial weakness and drooping of lower lip
- Mothers with CMD may give birth to severely affected infants who are immobile (clubfoot, contractures, poor fetal movement)
- Autosomal dominant caused by progressive expansion of a triplet repeat, GCT on chromosome 19q13.2-13.3 in a gene designated myotonin protein kinase
Congenital Myotonic Dystrophy

From Smith’s Recognizable Patterns of Human Malformation
Muscular Dystrophy

- Sex-linked recessive trait in 20-30:100,000 boys
- Presents around 3 yrs with inability to run properly or keep up athletically with peers
- Calf hypertrophy and proximal leg weakness: Gower sign
- Weakness progresses with arm weakness by 6 years and wheelchair confined by 12 years
- **Death due to pneumonia** or congestive heart failure from myocardial involvement
- Mild obesity and mild mental retardation may be present
- Absence of a large protein: Dystrophin Muscle biopsy shows muscle fiber degeneration and increased connective tissue
- Gene is Xp21 with deletions in this gene causing the disease in 80% of patients
OOPS!
Kind of better...
Metabolic Myopathies

- **Mitochondrial myopathies**: biopsy with ragged red fibers (collections of abnormal mitochondria), abnormalities along the respiratory chain, progressive diseases with both CNS and neuromuscular manifestations, increased serum lactate and calcifications of the basal ganglia

- **Nemaline myopathy**: 6 different genes (ACT1) facial/neck and shoulder/arm weakness, dysphagia and early diaphragmatic involvement

- **Endocrine myopathies**: corticosteroid administration, proximal muscle weakness (Critical illness myopathy with a triad of sepsis, steroids and paralysis (pancuronium)

- **Storage diseases**: Glycogen (Pompe): symmetric profound muscle weakness, cardiomegally, early diaphragm weakness, Carnitine deficiency: hypoglycemia, lethargy, muscle weakness and cardiomyopathy
Peripheral Neuropathy

- Charcot-Marie-Tooth (hereditary sensorimotor polyneuropathy) = abnormal myelin and/or axons
- Guillian-Barr Syndrome
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Acquired from other chronic diseases like diabetes, HIV, Vasculitis, effects of chemotherapy
Clinical Hallmarks

- Hypotonia
- Weakness
- Developmental delay, Motor regression
- **Pulmonary insufficiency**
- Cardiomyopathy
- Scoliosis, joint contractures
Pulmonary Manifestations

**Pathophysiology**
- Chest wall muscles
- Diaphragm
- Weak cough
- Aspiration risk
- Nocturnal hypoventilation

**Symptoms/signs**
- Bell-shaped, stiff
- Paradoxical pattern
- Dyspnea, pneumonia
- Pneumonia, wheeze
- Lethargy, snoring, arousals, headache
Respiratory Failure

Lung Failure

- Gas exchange failure manifested by hypoxemia

Pump Failure

- Ventilatory failure manifested by hypercarbia
  - Central depression
  - Mechanical defect
  - Fatigue
Respiratory Failure

Lung Failure

- Gas exchange failure manifested by hypoxemia

Pump Failure

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Lung failure

- Often the result of recurrent pneumonias secondary to chronic aspiration and/or GERD
- Swallowing is often affected leading to primary aspiration
- These issues over time can lead to chronic and end-stage lung disease/fibrosis
- Respiratory failure is the most common reason for early demise in patients with neuromuscular disease
Respiratory Failure

Lung Failure
- Gas exchange failure manifested by hypoxemia

Pump Failure
- Ventilatory failure manifested by hypercarbia
  - Central depression
  - Mechanical defect
  - Fatigue
Pump Failure

• Respiratory pump must move air against elastic and resistive forces on the lungs and chest wall
• Failure due to weak or fatigued respiratory muscles
• Failure due to increase load against this pump
Pump Failure

Factors that increase the respiratory load

• Studies in neuromuscular patients confirm that they have low lung compliance (i.e. they are stiff)
• Combination of factors like chronic aspiration probably account for this, kyphoscoliosis is also a factor in many patients
• The work of breathing is increased because of this low compliance
• Chest wall compliance is also low in these patients leading to increased work (abdominal compliance is increased but the net result is lower compliance overall)
Pump Failure in **Infants**

**Factors that increase the respiratory load**

- Infants with neuromuscular disease have **HIGH** chest wall compliance which leads to problems as well.
- The high compliance causes the chest wall to collapse due to the negative pleural pressures leading to the paradoxical breathing seen.
- This inefficient breathing leads to increased work (or load).
- There can also be collapse of the upper airway due to decreased tone causing obstruction during inspiration.
Mechanical defects:

- Weak and inefficient respiratory muscles causing paradoxical breathing
- On **inspiration** chest wall in/abd out infers weakness of intercostals OR chest wall out/abd in infers diaphragm weakness
- Muscle atrophy, disuse osteoporosis, contractures, kyphoscoliosis, cartilage changes
Pump Failure: Fatigue

Factors which affect the respiratory pump

- **Respiratory muscle fatigue**
- Inability to sustain a contractile force in the face of a constant load
- Tension time index of the diaphragm: ratio of the pressure during a given breath to the maximal pressure at occlusion time the duty cycle
- The higher the diaphragmatic pressure as a function of maximal pressure the diaphragm can sustain, the more likely the diaphragm is to fatigue
- If the inspiratory time is high relative to the total cycle time this will also lead to diaphragmatic fatigue
- Higher TTI in neuromuscular disease signifies a greater tendency toward respiratory muscle fatigue (almost entirely due to the elevated ratio of mean inspiratory pressure to max inspiratory pressure)
Tension Time Index (TTI)

• A measure of the likelihood that inspiratory muscle(s) will experience fatigue

• \( TT_{di} = \frac{P_{di}}{P_{di_{\text{max}}}} \cdot \frac{T_{i}}{T_{tot}} \)

\( P_{di} = \) mean transdiaphragmatic pressure on Inspiration
\( P_{di_{\text{max}}} = \) maximal transdiaphragmatic pressure
\( T_{i}/T_{tot} = \) duty cycle of the diaphragm, inspiratory Time divided by the total respiratory cycle time
Tension Time Index

Respiratory muscles

TTmus = Pmus / MIP \cdot Ti / Ttot

- **Pmus** is mean pressure generated by all respiratory muscles during inspiration (measured at the mouth)
- **MIP** is maximal inspiratory pressure measured at the mouth at FRC

- **Pmus** decreases due to:
  - Airway obstruction, parenchymal dse, hyperinflation

- **MIP** decreases due to:
  - Weakness, malnutrition

- **Ti** decreases due to:
  - Upper airway obstruction

- **Ttot** decreases due to:
  - Tachypnea
**Factors which affect the respiratory pump**

- Some evidence that respiratory drive may be affected since rebreathing CO$_2$ does not increase their ventilatory output.
- The degree of hypercapnia (chronic) is greater on average than would be expected from measure of muscle weakness (atelectasis, chest wall stiffness), though the weakness may not be able to increase drive to blow off CO$_2$.
- Gas exchange is aggravated by sleep and exercise.
Assessment of Respiratory Function in Neuromuscular Disease

- Pulmonary function testing
- Respiratory muscle strength
- Sleep studies
Assessment of Respiratory Function in Neuromuscular Disease: PFTs

- Restrictive disease
- Vital capacity markedly decreased and has prognostic implications: the age at which a patient reaches a VC of 1 liter (suggests 3 year survival in one study)
- Peak cough flow is being looked at as a way to follow strength over time
- Sniff pressures have been looked at and show good correlation between nose and mouth
PFTs and Duchenne MD

Recommended Yearly Studies

- Spirometry
- MIP/MEP
- Cough Peak Flow
- EtCO$_2$
- VBG/CBG
- (CBC, serum electrolytes, chest radiograph)
The respiratory management of patients with duchenne muscular dystrophy: A DMD care considerations working group specialty article

Step 1: Volume Recruitment / Deep Lung Inflation Technique

- Volume recruitment / deep lung inflation technique (by self-inflating manual ventilation bag or mechanical in-/exsufflation) when FVC < 40% predicted

Step 2: Manual and Mechanically Assisted Cough Techniques

Necessary when:
- Respiratory infection present and baseline peak cough flow < 270 lpm*
- Baseline peak cough flow < 150 lpm or max respiratory pressure < 40cm water
- Baseline FVC < 40% predicted OR < 1.25 liters in older teen / adult

Step 3: Nocturnal Ventilation

- Nighttime ventilation** is indicated in patients who have any of the following:
  - Signs or symptoms of hyperventilation (patients with FVC < 30% predicted are at especially high risk)
  - A baseline SaO2 < 90% and/or blood or end-tidal PC02 > 45 mmHg while awake
  - An apnea-hypopnea index ≥ 10/hour on polysomnography OR four or more episodes of SaO2 < 90% OR drops in SaO2 of at least 4% per hour of sleep

Note: Optimally, use of lung volume recruitment and assisted cough techniques should always precede initiation of non-invasive ventilation.

Step 4: Daytime Ventilation

In patients already using nocturnal assisted ventilation, daytime ventilation*** is indicated for:
- Self-extension of nocturnal ventilation into waking hours
- Abnormal apnea due to dyspnea, which is relieved by ventilatory assistance
- Inability to speak a full sentence without breathlessness, and/or
- Symptoms of hyperventilation with baseline SaO2 < 95% and/or blood or end-tidal PC02 > 45 mmHg while awake

Continuous non-invasive assisted ventilation (along with mechanically assisted cough) can facilitate endotracheal intubation for patients who were intubated during acute illness or during anesthesia, followed by weaning to nocturnal non-invasive assisted ventilation, if applicable.

Step 5: Tracheostomy

Indications for tracheostomy include:
- Patient and clinician preference****
- Patient cannot successfully use non-invasive ventilation
- Inability of the local medical infrastructure to support non-invasive ventilation
- Three failures to achieve intubation despite optimal use of noninvasive ventilation and mechanically assisted cough
- The failure of non-invasive methods of cough assistance to prevent aspiration of secretions into the lung and drops in oxygen saturation below 95% or the patient’s baseline, necessitating frequent direct tracheal suctioning via tracheostomy

**Recommended for nocturnal use: non-invasive ventilation with pressure support bilevel devices
***Recommended for daytime use: non-invasive ventilation with portable volume cycled or volume-pressure ventilators or combination volume-pressure ventilators
****Note: However, the panel advocates for the long-term use of non-invasive ventilators except in including 36 hours/day in eligible patients.
Respiratory Muscle Strength in Infants (MIP)

- Airway occlusion at FRC
- Occlusion maintained for 5 – 10 breaths
- Most negative inspiratory pressure taken as maximal
- Typically repeated in triplicate
Respiratory Muscle Strength in Infants (Peak Cough Flow)

- Can be measured with PFTs
- PCF < 270 lpm is associated with increased risk (surgery)
- Can be used as a predictor with MEP (< 60)

On our PFT machine take the FEF max and multiply by 60 sec to get LPM
Respiratory Muscle Strength (other maneuvers)

- Along with cough pressures one can monitor Vital capacity and TLC as the patient is able to do these maneuvers
- MIP ≥ 80 and MEP ≥ 90 excludes significant inspiratory and expiratory muscle weakness
- SNIP (Maximum sniff pressures) have been looked at and used by occluding one nostril
- SNIP normals are men ≥ 70 cm H2O and women ≥ 60 cm H2O
Nocturnal Ventilation

**Sleep**

- Prone to develop nocturnal hypoventilation
- Airway obstruction magnified during sleep with less upper airway control
- Nocturnal hypoxemia in the absence of daytime hypoxemia due to hypoventilation, low tidal volume, loss of intercostal muscle tone
- If end-expiratory lung volume drops below the volume at which there is closure of the small airways the result will be areas of low ventilation/perfusion as consequent hypoxemia

- **This can happen in asymptomatic patients**
- Polysomnograms suggested yearly for VC >60% MIP/MEP >60 and every 6 months if VC < 60% MIP/MEP <60
Indications for Polysomnography

- Pressure titration when on NPPV
- OSA evaluation (obesity, snoring, hypersomnolence)
- To seek sleep disordered breathing or hypoventilation in a: 1) symptomatic patient without daytime hypercapnia or severe PFT defect 2) Asymptomatic patient with daytime hypercapnia or severe PFT defect
Nocturnal Ventilation

Sleep

[Diagram showing the relationship between nocturnal ventilation and sleep disorders, including neuromuscular weakness, hyperventilation, pH retention, alveolar hypoventilation, periods of REM sleep, sleep deprivation, and daytime hypersomnolence and fatigue.]
Summary
Treatment Options

- **History**: time affected by neuromuscular changes, history of pneumonia, signs of aspiration (choking or gagging), quality of cough, symptoms of snoring, devices at home (oxygen, vest, cough assist, ventilator), airway hyper-reactivity, immunizations (influenza, RSV), nutritional issues, GERD symptoms
Treatment Options

- **Diet**: weight control (inactivity, reduced energy turnover in wasted muscle, misguided bulking up to increase muscle mass)
- Recommend high protein low cal diets to achieve ideal body weight which is lower than normals of the same age
- GTube when weight loss or aspiration issues are a problem
- Controlling constipation: bowel routine
Treatment Options

- **Oral secretions**: drooling and aspiration can be an issue when bulbar function becomes impaired
- Oral-Motor therapy
- Medications: scopalamine
- Surgical options: parotid duct ligation, transtympanic neurectomy, submandibular gland excision
Treatment Options

- **Swallowing dysfunction**: essential evaluation if aspiration is suspected by history
- Evaluation by speech therapy with different thicknesses
- If aspiration observed an effective cough is evaluated as well
- Nuclear medicine salivagram may be helpful as well
Treatment Options

- **Physiotherapy**: deep breathing, assisted cough, forced expiratory maneuvers
- Vest (ThAIRapy) has been useful though no studies out there
- **Inspiratory muscle training**: specific routine of respiratory muscle training correlated to endurance improvement (Topin, et al, 2002) Must start before muscle strength is very limited
Treatment Options

- **Scoliosis therapy**: complicated surgical challenge, multiple techniques used
- Improvement shown in vital capacity but overall decline not reduced
- If FVC is < 35% risk of complications approaches 50%
- Timing of surgery around substantial scoliosis and before severe muscle impairment
Kaplan-Meyer survivor plot to show the impact of spinal surgery and ventilation on survival. Curves show significant difference $p<0.0001$. Eagle, et al. 2007.
Mechanical Ventilation (NPPV)

- **Symptoms**: fatigue, dyspnea, morning HA
- **Physiologic criteria** (consensus statement)
  One of the following:
  1) PaCO2 > 45 (50) mm Hg
  2) Nocturnal oximetry with O₂ saturation <85% for >5 consecutive minutes
  3) Maximal inspiratory pressure < 60 cm H₂O OR FVC < 50% predicted
Non-Invasive ventilation: BIPAP
Mechanical Ventilation (NPPV)

- **Goals**: alleviate symptoms, improve alveolar ventilation, improve sleep quality, enhance quality of life, decrease pulmonary complications, reduce hospitalizations, postpone tracheostomy and prolong survival

- **Contraindications**: upper airway obstruction, uncontrollable secretions, uncooperative patient, inability to fit interface, inability to achieve adequate peak cough flows even with assistance

- **BIPAP is appropriate**, CPAP may not be indicated
INVASIVE RESPIRATORY CARE

• Intubation (in an acute illness)
• Tracheostomy with ventilator support
Mechanical Ventilation (Invasive)

- Obviously a last resort or patient preference
- Used when NPPV is required nearly continuously
- Every attempt should be made to make this as easy as possible for patient to continue to talk and swallow if possible
- Daytime sipper may be used to extend use of NPPV
Invasive Ventilation
A couple of things they need
SMA
Special considerations

• Anticipatory respiratory care, early use of BIPAP
• Chronic management and family goals discussed EARLY
• Airway clearance physiotherapy and cough assist, use of oximetry in the home early use of chest clearance if patient deviates from baseline
• Non-sitters (vs sitters and standers)
• Gastrointestinal dysfunction: GERD, abdominal distention, particular vulnerability to fasting and catabolic states (hypoglycemia in the face of muscle wasting especially in acute illness), early GT/Nissen use
• Prompt caloric supplementation needed ASAP
DMD

Special Considerations

• Consider sleep evaluations early
• End of life directives/providing the information
• Malnutrition and obesity are equally prevalent in DMD
• Don’t forget cardiac involvement: second most common cause of death (dilated cardiomyopathy, arrhythmias)
• Daytime and nighttime non-invasive ventilation or continuous invasive ventilation
SMA Type 1 7.5 months S/P Gene Therapy
End of Life Care

• Palliative care
• Hospice Care
References


• Panitch, HB. Respiratory issues in the management of children with neuromuscular disease. Resp Care, 51, 885-93, 2006