Neuromuscular in the Pediatric Clinic: Recognition and Referral

Matthew Harmelink, MD
Assistant Professor, Pediatric Neurology
Medical College of Wisconsin
Objectives:

1. Understand common presentations of pediatric neuromuscular diseases
2. Understand the reason and how to refer patients with possible neuromuscular disease
3. Understand the upcoming treatments for neuromuscular diseases
Disclosures

• Advisory Board for Biogen- Nusinersen for SMA
About Me

• Undergraduate: UW-Madison
• Medical School: Medical College of Wisconsin
• Pediatric Residency: University of California-Irvine
• Child Neurology Fellowship: Medical College of Wisconsin
• Neuromuscular Fellowship: UCLA
Definition

- Neuromuscular Disease- any disease that affects the peripheral nerve, muscle or connective structures of muscle
- Motor- starts in the alpha motor neuron to the effector organ and surrounding tissue
- Sensory- from the extremity and receptor to the entry into the spinal cord
Peripheral Nerves

1. Stretching stimulates SENSORY RECEPTOR (muscle spindle)
2. SENSORY NEURON excited
3. Within INTEGRATING CENTER (spinal cord), sensory neuron activates motor neuron
4. MOTOR NEURON excited
5. EFFECTOR (same muscle) contracts and relieves the stretching

Motor neuron to antagonistic muscles is inhibited
Antagonistic muscles relax

To brain
Inhibitory interneuron

http://pixgood.com/monosynaptic-reflex-arc.html
Muscle/Nerve Components

http://www.austincc.edu/apreview/PhysText/PNSefferent.html
Definitions

• Neuropathy
  – A disease affecting the nerve

• Myopathy
  – A disease affecting the muscle, typically the contractile apparatus or energy production

• Dystrophy
  – A disease affecting the structures connecting the cytoskeleton of muscle to the sarcolemma to extra connective structures
Definitions

- Dystrophy vs. Myopathy
  - Most dystrophies are progressive
  - Less ophthalmologic involvement
  - More organs involved in dystrophy but maybe less brain involvement
Muscle Components

Figure 1: Sarcolemma and proteins involved in muscular dystrophies
DG=dystroglycan, SP=sarcospan, SY=syntrophin, DYB=dystrobrevin, Pa-papillin, T=talin, V=vinculin, FAK=focal adhesion kinase. Not all proteins mentioned in this figure are primarily affected by muscular dystrophies.
Done with Anatomy
Laboratory and Electrical Testing

• Value of a Creatine Kinase
  – Creatine Kinase helps include neuromuscular disease

  • Normal CK does not exclude myopathy

  • Mildly elevated CK can be from Neuropathy (such as in SMA type 1)
    – Worse if the disease is severe
### Table 4
Pediatric reference ranges for creatine kinase

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th></th>
<th></th>
<th>Female</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>U/L</td>
<td></td>
<td>n</td>
<td>U/L</td>
<td></td>
</tr>
<tr>
<td>0–90 d</td>
<td>71</td>
<td>28–300</td>
<td></td>
<td>65</td>
<td>42–470</td>
<td></td>
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<tr>
<td>3–12 mo</td>
<td>129</td>
<td>24–170</td>
<td></td>
<td>90</td>
<td>26–240</td>
<td></td>
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<tr>
<td>13–24 mo</td>
<td>121</td>
<td>27–160</td>
<td></td>
<td>120</td>
<td>24–175</td>
<td></td>
</tr>
<tr>
<td>2–10 y</td>
<td>245</td>
<td>30–150</td>
<td></td>
<td>231</td>
<td>24–175</td>
<td></td>
</tr>
<tr>
<td>11–14 y</td>
<td>86</td>
<td>30–150</td>
<td></td>
<td>77</td>
<td>30–170</td>
<td></td>
</tr>
<tr>
<td>15–18 y</td>
<td>56</td>
<td>33–145</td>
<td></td>
<td>111</td>
<td>27–140</td>
<td></td>
</tr>
</tbody>
</table>

Pediatric Reference Ranges for Creatine Kinase,
CKMB, Troponin I, Iron, and Cortisol

STEWEN J. SOLDIN,*† JAYASIMHA N. MURTHY,*† PANKAJ K. AGARWALLA,*† OLUIMIDE OJERO, and JENNIFER CHEA*†
Establishment of pediatric reference intervals on a large cohort of healthy children

Emma K. Southcott a, Jennifer L. Kerrigan a, Julia M. Potter a,b, Richard D. Telford b,c, Paul Waring d, Graham J. Reynolds b,e, Antony R.A. Lafferty b,e, Peter E. Hickman a,b,*

Clinica Chimica Acta 411 (2010) 1421–1427

Table 2
Mean, median and 95% reference intervals for selected analytes.

<table>
<thead>
<tr>
<th>Age group</th>
<th>N</th>
<th>Boys Mean</th>
<th>Median</th>
<th>RI</th>
<th>N</th>
<th>Girls Mean</th>
<th>Median</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine kinase (U/L)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months−2 y</td>
<td>150</td>
<td>138</td>
<td>127</td>
<td>50−272</td>
<td>122</td>
<td>119</td>
<td>110</td>
<td>0.002</td>
</tr>
<tr>
<td>3−5 y</td>
<td>149</td>
<td>117</td>
<td>102</td>
<td>59−296</td>
<td>150</td>
<td>99</td>
<td>93</td>
<td>0.005</td>
</tr>
<tr>
<td>6−8 y</td>
<td>149</td>
<td>117</td>
<td>102</td>
<td>54−275</td>
<td>149</td>
<td>112</td>
<td>106</td>
<td>NS</td>
</tr>
<tr>
<td>9−11 y</td>
<td>150</td>
<td>135</td>
<td>122</td>
<td>55−324</td>
<td>148</td>
<td>113</td>
<td>102</td>
<td>&lt;0.001</td>
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<tr>
<td>12−14 y</td>
<td>148</td>
<td>154</td>
<td>131</td>
<td>63−407</td>
<td>149</td>
<td>104</td>
<td>93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>15−17 y</td>
<td>149</td>
<td>213</td>
<td>159</td>
<td>68−914</td>
<td>144</td>
<td>118</td>
<td>94</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Short communication

Age and gender specific pediatric reference intervals for aldolase, amylase, ceruloplasmin, creatine kinase, pancreatic amylase, prealbumin, and uric acid

Sarah M. Clifford a, Ashley M. Bunker b, Jeffrey R. Jacobsen c, William L. Roberts a,b,*

Clinica Chimica Acta 412 (2011) 788–794
Laboratory and Electrical Testing

<table>
<thead>
<tr>
<th>TABLE IV</th>
<th>Men*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blacks (n = 57)</td>
</tr>
<tr>
<td><strong>Biochemical data</strong></td>
<td></td>
</tr>
<tr>
<td>Total creatine kinase (units/liter)</td>
<td>146.5 ± 136.9†</td>
</tr>
<tr>
<td>Median creatine kinase (units/liter)</td>
<td>108</td>
</tr>
<tr>
<td>Subjects with abnormal creatine kinase values</td>
<td>37 (64.9%)†</td>
</tr>
<tr>
<td>Potassium (meq/liter)</td>
<td>4.23 ± 0.48</td>
</tr>
<tr>
<td>(n = 38)</td>
<td>(n = 25)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.14 ± 0.40</td>
</tr>
<tr>
<td>(n = 38)</td>
<td>(n = 25)</td>
</tr>
</tbody>
</table>

Racial Differences in Serum Creatine Kinase Levels

HENRY R. BLACK, M.D.
HELEN OULLICH, B.A.
CYNDIE B. GARELICK, M.P.H.
New Haven, Connecticut
September 1986 The American Journal of Medicine Volume 81
Figure 1. Mean plasma creatine kinase levels in males (left panel) and females (right panel); values are the mean ± SD; N represents the number of subjects studied.
Laboratory and Electrical Testing

• Value of a Creatine Kinase
  – Creatine Kinase
    • Also will vary by activity
    • Abnormally high ranges
      – Dystrophies
        » Ranges from normal to >100x normal
Laboratory and Electrical Testing

- Last note about Creatine Kinase
  - Rhabdomyolysis and muscle disease
    - Very uncommon despite CK >30k in some patients or increases from 5K to >30k with activity
    - Not certain why exactly
    - Do I check a BMP if the patient is having worsening pain and CK jumps? Yes
    - Do I often check CKs in patients with muscle disease and leg pain? No
Electromyography and Nerve Conduction Studies

- What is this?
  - 2 Parts:
    - Nerve Conduction Study
      - Use electrical Activity to measure conduction through the nerve
      - Helps to delineate if a nerve is involved
        » Can differentiate demyelinating and axonal
    - Electromyography (EMG)
      - A needle exam to test muscle insertion, resting and activating electrical activity
Electromyography and Nerve Conduction Studies

• When you order:
  – Number of limbs etc… doesn’t matter that much
    • We’ll do what we need anyways
  – We do a brief history and exam
  – If unsure, best to ask for neuromuscular consult with EMG
Electromyography and Nerve Conduction Studies

- Diagnostic Yield
  - Timing is everything

<table>
<thead>
<tr>
<th>Time after lesion</th>
<th>Insertional activity</th>
<th>Fibrillation potentials</th>
<th>Recruitment</th>
<th>Amplitude/duration</th>
<th>Shape</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (&lt;14 days)</td>
<td>Normal</td>
<td>Absent</td>
<td>Reduced</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Subacute</td>
<td>Increased</td>
<td>Present</td>
<td>Reduced</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>(14–21 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent (1–3 months)</td>
<td>Increased</td>
<td>Present (maximal)</td>
<td>Reduced</td>
<td>May increase</td>
<td>Polyphasic</td>
</tr>
<tr>
<td>Chronic (&gt;6 months)</td>
<td>May be increased</td>
<td>Present but fewer</td>
<td>Reduced</td>
<td>Increased</td>
<td>Polyphasic</td>
</tr>
</tbody>
</table>
Electromyography and Nerve Conduction Studies

• What it tells us
  – We can determine if the disease is neuropathic or myopathic/dystrophic
  – Determine staging of neuropathy
  – See if there is irritability (inflammatory disease, active demyelination)
  – Some special sounds to determine special diseases (myotonia)
Muscle Biopsy

- **To Diagnosis… or Not**
  - Traditionally diseases are called their pathologic disease names
    - Centronuclear Myopathy
    - Nemaline Rod Myopathy

- **Upcoming is to diagnosis based upon genetic results**
  - Many pathologies and genes overlap
# Muscle Biopsy

<table>
<thead>
<tr>
<th>Structural defect</th>
<th>Genes</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rods</td>
<td>ACTA1, NEB, TPM2, TPM3, TNNT1, CFL2, KBTBD13, KLHL40</td>
<td>Nemaline myopathies</td>
</tr>
<tr>
<td>Core</td>
<td>RYR1, SEPN1, ACTA1, TTN, MYH7, KBTBD13</td>
<td>Core myopathies</td>
</tr>
<tr>
<td>Central nuclei</td>
<td>MTM1, DNM2, BIN1, RYR1, (DM1)</td>
<td>Centronuclear myopathies</td>
</tr>
<tr>
<td>Rods and cores</td>
<td>RYR1, NEB, KBTBD13, CFL2</td>
<td>Core-rod myopathy</td>
</tr>
<tr>
<td>Caps</td>
<td>TPM2, TPM3, ACTA1</td>
<td>Cap disease</td>
</tr>
<tr>
<td>Congenital fibre type disproportion</td>
<td>ACTA1, TPM3, TPM2, RYR1, SEPN1</td>
<td></td>
</tr>
<tr>
<td>Distal myopathy no rods</td>
<td>NEB</td>
<td></td>
</tr>
<tr>
<td>Distal arthrogryposis</td>
<td>TPM2, MYH3, MYH8, TNNT12, TNNT3</td>
<td></td>
</tr>
</tbody>
</table>

*Approach to the diagnosis of congenital myopathies*[^1]  
Testing: The Next Step

• MRI and Ultrasound
  – There is literature and some places are using MRI of muscle (specifically the thigh) and/or Ultrasound to help with diagnosis
  – Jury is still out for me on effectiveness for me
    • Looking forward to hearing more about it
The Next Step
Change of Pace

• Lets look at common ages and approaches
  – We’ll start young
  – I’ll hit some highlights of things I’ve learned or found useful
Hypotonic Infant

- Epidemiology:
  - 80% of all infantile hypotonia is central/genetic
  - 20% is neuromuscular

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Central</td>
<td>82%</td>
</tr>
<tr>
<td>Hypoxic/Ischemic or Hemorrhagic Injury</td>
<td>34%</td>
</tr>
<tr>
<td>Chromosomal or Genetic Syndromes</td>
<td>26%</td>
</tr>
<tr>
<td>Brain Malformations</td>
<td>13%</td>
</tr>
<tr>
<td>Neurometabolic or neuroendocrinologic</td>
<td>9%</td>
</tr>
<tr>
<td>Periphereal</td>
<td>18%</td>
</tr>
<tr>
<td>Spinal Muscular Atrophy</td>
<td>6%</td>
</tr>
<tr>
<td>Myotonic Dystrophy</td>
<td>4%</td>
</tr>
<tr>
<td>Other</td>
<td>8%</td>
</tr>
</tbody>
</table>

Etiology of Infant Hypotonia Based Upon Localization

Hypotonic Infant

• Prenatally:
  – 78% of infants with polyhydramnios and/or decreased fetal movements were born with hypotonia
  – But…
• Only 12.7% of mothers who had infants with hypotonia reported decreased fetal movements
Hypotonic Infant

• How good are we at localizing:
  – 1st time child neurologist exam:
    • PPV if called central 86%
    • PPV if called peripheral 52%
  – Why:
    • 88% of patients with peripheral hypotonia had decreased or absent reflexes versus 36% of the central group
    • In SMA, 75% of infants have some absent reflexes


Table 3 Contribution of standard diagnostic tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Total</th>
<th>Contributive</th>
<th>Normal or non-specific</th>
<th>Misleading or contradictory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroimaging</td>
<td>124</td>
<td>50 (40%)</td>
<td>69 (56%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>EEG</td>
<td>92</td>
<td>35 (38%)</td>
<td>53 (58%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Molecular biology</td>
<td>43</td>
<td>18 (42%)</td>
<td>25 (58%)</td>
<td>0</td>
</tr>
<tr>
<td>Karyotype analysis</td>
<td>59</td>
<td>24 (41%)</td>
<td>35 (59%)</td>
<td>0</td>
</tr>
<tr>
<td>NCS/EMG</td>
<td>23</td>
<td>10 (43.5%)</td>
<td>10 (43.5%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Muscle biopsy</td>
<td>14</td>
<td>6 (43%)</td>
<td>6 (43%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Neostigmine test</td>
<td>10</td>
<td>0</td>
<td>10 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Metabolic investigations</td>
<td>45</td>
<td>9 (20%)</td>
<td>36 (80%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Prospective Study of Spinal Muscular Atrophy Before Age 6 Years

Susan T. Iannaccone, MD*, Richard H. Browne, PhD†, Frederick J. Samaha, MD‡, C. Ralph Buncher, ScD§, and DCN/SMA Group

Table 5. Deep tendon reflex pattern in SMA patients

<table>
<thead>
<tr>
<th>Deep Tendon Reflexes</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Absent</td>
<td>43 (74%)</td>
</tr>
<tr>
<td>Decreased distally</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Decreased lower extremities</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Decreased mixed</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (3%)</td>
</tr>
<tr>
<td><strong>Totals:</strong></td>
<td>58 (100%)</td>
</tr>
</tbody>
</table>

Table 2. Relationship between age of onset and death

<table>
<thead>
<tr>
<th>Status*</th>
<th>Onset of First SMA Symptoms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-3 mos</td>
<td>4-5 mos</td>
</tr>
<tr>
<td>Alive</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Dead</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Totals:</td>
<td>15</td>
<td>12</td>
</tr>
</tbody>
</table>

* As of April, 1992.

Spinal Muscular Atrophy

• Classic SMA
  – Secondary to SMN1 gene deletion on 5q chromosome (autosomal recessive)
    • SMN2 modulates - not clinically relevant
  – 5 types: 0 to 4

• None Classic SMA:
  – Last I checked there were >45 reported versions presenting at different ages
    • Many are very rare
Spinal Muscular Atrophy

• Upcoming Therapies:
  – Lots of trials including valproic acid (in vitro up regulated SMN)
  – Most positive is a adenoassociated viral vector 9 intrathecal study
    • Phase 1 trial started April 2014 for SMA type 1
Spinal Muscular Atrophy

• In animal models, staining for SMN was found not only in anterior horn cells but..
  – Hippocampus, cerebellum deep nuclei and thalamus amongst more

• A small group also evaluated fatty acid oxidation and found a unique pattern of elevated dicarboxylic aciduria that was noted only in moderate to severe patients
  – Small autopsy studies show fatty livers in severe some severe cases
Abnormal Toddler

• History:
  – Crawling/Walking
    • When is as important as how
  – Most children start walking with a wide-based gait
    • Should narrow after 3 months (some argue up to 5 months in PT literature)
Abnormal Toddler Gait

- Exam:
  - Watch the calves
  - Watch their gait
  - How do they get up off the floor
Cramping in a Child

• Cramping is not congruent with metabolic myopathy

  – Almost all of our neuromuscular patient’s “cramp”
    • Is it cramping or soreness?
    • Is it during activity or after activity- if so when?
    • Does it affect their activity?
Dystrophies

• Duchenne’s Muscular Dystrophy
  – X-linked
  – Longest human gene with 79 exon
  – Progressive disease

  – Very high CK (typically >10-30x normal)
  – Progressive with loss of gait by age 12 at latest
  – Cardiac and cognitive involvement
Dystrophies

• Becker’s Muscular Dystrophy
  – Variable age of onset
  – Elevated CK (typically at least >5x)
  – May retain ambulation
  – Cardiac involvement

• X-Linked Cardiomyopathy
  – Carriers of the dystrophin gene, or those affected (young men)
Dystrophies

• Treatment:
  – Mainstay is steroid therapy
    • Improved duration of ambulation, pulmonary and cardiac function
    • Patients continue to progress
  – Upcoming Therapy
    • Many gene trials
    • Difficulty is that each exon needs a trial and drug
    • The gene is too long to replace
Dystrophies

• Next step:
  – If treatments are effective do we consider adding this to the newborn screen

• Incidence of 1 in 5,000 to 1 in 15,000
Teenager

• History:
  – How long… not the symptoms but everything else?
    • If they come with “cramping”, how long have they had trouble walking up stairs, brushing their hair ect…

  – Videos and photos are key
Teenager

• Examination:
  – Gower’s sign:
    • Sign of proximal muscle weakness (not neuromuscular disease)
  – Running:
    • Look for ability to raise both feet of floor as well as speed
    • Look at base length
    • Look for Trendelenburg versus foot drop
  – Walking:
    • Walk on toes (gastronemius complex weakness)
    • Walk on heels (tibialis anterior weakness)
Teenager

- Examination:
  - Test for “coordination”
    - Mild weakness can present as “ataxia” but when you support the limb it resolves due to weakness
  - Myopathic Facies
  - High Arched Palate
Teenager

- Examination:
  - Special Techniques:
  - Neuromuscular Junction:
    - Ptosis
      - Sustained upward gaze for 1-2 minutes
      - If ptosis worsens- sign of neuromuscular disease
    - Fatigability:
      - Squeeze and relax hands- look for decreasing grip strength
Myasthenia Gravis
Teenager

- Slowly progressive Muscular Dystrophies
  - Fascioscapulohumeral Muscular Dystrophy
  - Limb Girdle Muscular Dystrophies
  - Emery Dryfuss Muscular Dystrophy
  - Ect…

- Myopathies

- Neuromuscular Junction Deficits
Myasthenia Gravis

- Autoimmune Type
  - VS.
- Congenital Type
# Myasthenia Gravis

<table>
<thead>
<tr>
<th>Table 1: Comparisons of prepubertal and postpubertal features of JMG.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male : female ratio</strong></td>
</tr>
<tr>
<td>M = F</td>
</tr>
<tr>
<td>Patients with AChR antibodies detected in generalised disease</td>
</tr>
<tr>
<td>Ocular presentation</td>
</tr>
<tr>
<td>Chinese</td>
</tr>
<tr>
<td>Progression of OMG to generalised MG</td>
</tr>
<tr>
<td>Remission (spontaneous or with treatment)</td>
</tr>
</tbody>
</table>
Myasthenia Gravis

• First line:
  – Cholinesterase Inhibitor

• Second line:
  – Steroids
  – Steroid Sparing Agents

• Consider Thymectomy
Myasthenia Gravis

• Drooping eyelids
  – Don’t forget other diseases
    • Progressive External Ophthalmoplegia
    • Kearn-Sayre’s Syndrome
    • Myopathies
My last minute Plug

- If you want us to see patients:
  - Better sooner than later- love to see patients before the EMG or biopsy to help assist for any of these diseases
  - We see neuromuscular patients in clinic- just check the referral box
  - We have a full multidisciplinary clinic for Muscular Dystrophy Clinic for our diagnosed patients
    - Neurology, PM&R, Cardiology, Pulmonary, PT, Equipment, and MDA representative
Neuromuscular Diseases are diverse

Where for many disease there aren’t treatments or cures, the next decade is going to be fascinating for neuromuscular disease

- New Testing
- New Treatments
- New Diseases
Thank you