An Overview of Pediatric Neuromuscular Disease

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Disclosures

• No disclosures or conflict of interest
CNS influences the activity of skeletal muscle through two sets of neurons

- Upper motor neuron
- Lower motor neuron
Relationship of UMN to LMN

• Upper motor neurons control the lower motor neurons through two different pathways:
  - Pyramidal tracts (corticospinal tracts)
  - Extrapyramidal tract
The Motor Unit

Motor Neuron

Axon

NMJ

Diseases of motor neurons

Peripheral neuropathies

Diseases of neuromuscular transmission

Primary muscle disease: myopathies

Motor Neuron

IPS 2017
Overview of Ped NM Disease

**Anterior Horn Cell**
- Hereditary
  - Spinal Muscular Atrophy
- Acquired
  - Poliomyelitis

**Nerve Fibre**
- Neuropathies
  - a) Demyelinating eg GBS.
  - b) Axonal, eg lead.

**Neuromuscular Junction**
- Myasthenia gravis

**Muscle**
- Hereditary
  - 1. Muscular Dystrophy
  - 2. Congenital Myopathies
- Acquired
  - 1. Dermatomyositis.
  - 2. Endocrine myopathies.
<table>
<thead>
<tr>
<th>Feature</th>
<th>Neuropathic</th>
<th>Myopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution of weakness</td>
<td>Distal (length dependent)</td>
<td>Proximal (may involve face or eyes)</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Absent</td>
<td>Usually present/reduced</td>
</tr>
<tr>
<td>Sensory loss</td>
<td>Usually present</td>
<td>Absent</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Present</td>
<td>Absent until late (pseudohypertrophy)</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>Normal to mildly elevated</td>
<td>Elevated (may be normal)</td>
</tr>
<tr>
<td>Nerve conduction velocity</td>
<td>Usually decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>EMG</td>
<td>Fibrillations and fasciculations</td>
<td>Small muscle units</td>
</tr>
<tr>
<td>Muscle biopsy</td>
<td>Group atrophy</td>
<td>Irregular necrotic fibers</td>
</tr>
</tbody>
</table>
Presenting Symptoms

- Motor developmental delay
- Gait characteristics
- Functional difficulties
## Table 2  Symptoms and Signs Associated with Myopathies

<table>
<thead>
<tr>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>Myalgias</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Cramps</td>
</tr>
<tr>
<td>Exercise intolerance</td>
<td>Contractures</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>Myotonia</td>
</tr>
<tr>
<td></td>
<td>Myoglobinuria</td>
</tr>
</tbody>
</table>

Jackson C. Semin Neurol 2008;28:228–240
<table>
<thead>
<tr>
<th>Location</th>
<th>Signs or Symptoms of Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial</td>
<td>Inability to “bury eyelashes,” “horizontal smile,” inability to whistle</td>
</tr>
<tr>
<td>Ocular</td>
<td>Double vision, ptosis, dysconjugate eye movements</td>
</tr>
<tr>
<td>Bulbar</td>
<td>Nasal speech, weak cry, nasal regurgitation of liquids, poor suck, difficulty swallowing, recurrent aspiration pneumonia, cough during meals</td>
</tr>
<tr>
<td>Neck</td>
<td>Poor head control</td>
</tr>
<tr>
<td>Trunk</td>
<td>Scoliosis, lumbar lordosis, protuberant abdomen, difficulty sitting up</td>
</tr>
<tr>
<td>Shoulder girdle</td>
<td>Difficulty lifting objects overhead, scapular winging</td>
</tr>
<tr>
<td>Forearm/hand</td>
<td>Inability to make a tight fist, finger or wrist drop</td>
</tr>
<tr>
<td>Pelvic girdle</td>
<td>Difficulty climbing stairs, waddling gait, Gower’s sign</td>
</tr>
<tr>
<td>Leg/foot</td>
<td>Foot drop, inability to walk on heels or toes</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Use of accessory muscles</td>
</tr>
</tbody>
</table>
Signs of Neuromuscular Disease

- **Observation**
  - Atrophy or hypertrophy
  - Fasciculations
  - Functional abilities

- **Palpation**
  - Muscle texture
  - Tenderness
  - Nerve thickness

- **Examination**
  - Joint contractures
  - Myotonia
  - Strength
  - Patterns of weakness
  - Gower sign
  - Tendon reflexes
Gower Sign
Classification of Pediatric Myopathies

- Muscular dystrophies
- Congenital myopathies
- Inflammatory myopathies
- Metabolic myopathies
- Channelopathies
- Myasthenic syndromes
Muscular Dystrophy: Classification

**X-linked recessive**
- Duchenne/Becker muscular dystrophy
- Emery-Dreifuss muscular dystrophy

**Autosomal dominant**
- Limb girdle muscular dystrophy (type 1)
- Emery-Dreifuss muscular dystrophy
- Myotonic dystrophy
- Facio-scapulo-humeral muscular dystrophy

**Autosomal recessive**
- Limb girdle muscular dystrophy (type 2)
- Congenital muscular dystrophy
Definition of Muscular Dystrophy

- Group of genetically determined disorders
- Progressive degenerative process in skeletal muscle
- Unifying feature is the histological appearance on muscle biopsy

Courtesy of Dr. Susan Stagautis
Pattern of Weakness

A: 
B: 
C: 
D: 
E: 

Pattern of Weakness

A: Duchenne/Becker
B: Emery-Dreifuss
C: Limb girdle
D: Facioscapulohumeral
E: Distal

Duchenne/Becker Muscular Dystrophy

- Progressive, symmetric proximal weakness
- Calf hypertrophy (pseudohypertrophy)
- Gower sign
- Waddling gait typically with toe-walking
- Hypo/areflexia
- Tendoachilles contractures
- Scoliosis (usually later in disease course)
<table>
<thead>
<tr>
<th></th>
<th>DUCHENNE</th>
<th>BECKER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>1:3 500 live male births</td>
<td>1:30 000 live male births</td>
</tr>
<tr>
<td><strong>Age of presentation</strong></td>
<td>3-5 yrs</td>
<td>5-10 yrs, sometimes adolescence</td>
</tr>
<tr>
<td><strong>Loss of ambulation</strong></td>
<td>Before 13th birthday</td>
<td>Beyond 16th birthday</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>Early 20’s – from cardiopulmonary failure</td>
<td>Variable – long term survival possible</td>
</tr>
<tr>
<td><strong>CK</strong></td>
<td>Massively elevated &gt; 10-100 X normal</td>
<td>Massively elevated &gt; 10-100 X normal</td>
</tr>
<tr>
<td><strong>Cardiomyopathy</strong></td>
<td>Late – end stage</td>
<td>Early, disproportionate to muscle weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be presenting feature</td>
</tr>
<tr>
<td><strong>Dystrophin</strong></td>
<td>Absent (&lt; 5%)</td>
<td>Reduced in quantity or quality (&gt; 10%)</td>
</tr>
<tr>
<td><strong>Gene deletion</strong></td>
<td>About 97% of cases</td>
<td>About 97% of cases</td>
</tr>
</tbody>
</table>
Diagnosis?
Limb Girdle Muscular Dystrophy

Clinical Presentation

• Variable age of onset – infancy, childhood, adolescence or even adult life.
• Progressive predominant proximal shoulder and hip girdle weakness and wasting.
  - Face typically not involved (may be involved late in disease)
• Calf hypertrophy is frequently seen, especially in the sarcoglycanopathies
• Tendoachilles contractures common
  - other joint contractures usually only occurs in severe or advanced disease.
• Variable cardiac involvement
### Autosomal Dominant

<table>
<thead>
<tr>
<th>LGMD1A</th>
<th>5q31</th>
<th>Myotilin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGMD1B</td>
<td>1q21.2</td>
<td>Lamin A/C</td>
</tr>
<tr>
<td>LGMD1C</td>
<td>3p25</td>
<td>Caveolin*</td>
</tr>
<tr>
<td>LGMD1D</td>
<td>7q</td>
<td>HSP</td>
</tr>
<tr>
<td>LGMD1E</td>
<td>6q23</td>
<td>Desmin</td>
</tr>
<tr>
<td>LGMD1F</td>
<td>7q32</td>
<td>Transportin 3</td>
</tr>
<tr>
<td>LGMD1G</td>
<td>4q21</td>
<td></td>
</tr>
</tbody>
</table>

### Autosomal Recessive

<table>
<thead>
<tr>
<th>LGMD2A</th>
<th>15q</th>
<th>Calpain*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGMD2B</td>
<td>2p13</td>
<td>Dysferlin*</td>
</tr>
<tr>
<td>LGMD2C</td>
<td>13q12</td>
<td>γ-sarcoglycan</td>
</tr>
<tr>
<td>LGMD2D</td>
<td>17q 12</td>
<td>α-sarcoglycan</td>
</tr>
<tr>
<td>LGMD2E</td>
<td>4q12</td>
<td>β-sarcoglycan</td>
</tr>
<tr>
<td>LGMD2F</td>
<td>5q33</td>
<td>δ-sarcoglycan</td>
</tr>
<tr>
<td>LGMD2G</td>
<td>17q12</td>
<td>Telethonin</td>
</tr>
<tr>
<td>LGMD2H</td>
<td>9q</td>
<td>E3-ubiquitin ligase</td>
</tr>
<tr>
<td>LGMD2I</td>
<td>19q13.3</td>
<td>Fukutin-related protein</td>
</tr>
<tr>
<td>LGMD2J</td>
<td>2q24.3</td>
<td>Titin2</td>
</tr>
<tr>
<td>LGMD2X</td>
<td>6q21</td>
<td></td>
</tr>
</tbody>
</table>

*May preset with “benign hyperCKemia”

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From Bönneman et al. *Current Opinion in Pediatrics* 1996; 8: 569 – 582
LGMD2B: Dysferlin
LGMD2C: Gamma-sarcoglycan
LGMD 2F: Delta sarcoglycan

Courtesy of Dr. Carsten Bonnemann
Diagnosis?
Emery-Dreifuss Muscular Dystrophy

• Triad:
  — Contractures:
    — elbows, tendoachilles, spine
  — Weakness:
    — humeroperoneal pattern/distribution
  — Cardiac involvement:
    — conduction defects (atrial paralysis, ventricular arrhythmias) and cardiomyopathy

• Genetics:
  — X-linked and autosomal dominant
Diagnosis?
Overview of Ped NM Disease
Facioscapulohumeral Muscular Dystrophy

- FSHD is probably the third most common form of muscular dystrophy.
- **Genetics:** partial deletion of a tandem repeat in the subtelomeric region of chromosome 4q.
Clinical Presentation

- Age of onset, disease severity and distribution of muscle weakness can be variable both within and between families
  - Typically early involvement of facial and scapular muscles, descending to involve biceps, triceps and eventually pelvic girdle muscles.
  - The *exception* to this is the early involvement of the tibialis anterior muscle.
  - An *asymmetric* pattern of muscle involvement is frequent and often striking.
    - Bulbar, extraocular, masseter, temporalis and respiratory muscles are usually spared

- **CK** – variable (elevated in about ~50%)
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- Congenital muscular dystrophy
Overview

• Clinically and genetically heterogeneous
• Autosomal recessive inheritance
  - At least 9 genes identified to date
• CK – variable (normal to very high)
Clinical Presentation

- Typically presents at birth or within first few months of life
- Hypotonia, weakness, hyporeflexia, joint contractures
- May present with delayed motor milestones during infancy
CNS Involvement

- CNS involvement may occur (CMD +)
  - Lissencephaly
  - White matter changes
Ullrich muscular dystrophy
Cleveland Clinic

Every life deserves world class care.