OBJECTIVES
1. Formulate an approach and provide a differential diagnosis of the child with weakness.
2. Review the clinical features of the more common muscular dystrophies.
3. Diagnostic approach to the genetic work up of the more common muscular dystrophies.

Classification
- Muscular dystrophies
- Congenital myopathies
- Inflammatory myopathies
- Metabolic myopathies
- Channelopathies
- Myasthenic syndromes
**Definition of Muscular Dystrophy**

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

**Myopathic Changes**

- Necrosis & phagocytosis
- Degeneration
- Regeneration
- Fiber splitting & fibrosis

**Question 1**

The following are all inherited as an X-linked recessive trait EXCEPT:

a. Duchenne muscular dystrophy
b. Becker muscular dystrophy
c. Emery-Dreifuss muscular dystrophy
d. Myotonic dystrophy
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
- Oculopharyngeal muscular dystrophy

Autosomal recessive
- Limb girdle muscular dystrophy (type 2)
- Congenital muscular dystrophy

Question 2

• A 4 year old boy presents to your office for evaluation of toe-walking and frequent falling since about 2 years of age. Parents have also noticed that he gets up from the floor in an unusual pattern. Mother’s brother died in his early 20’s from a similar problem.
• Examination shows pelvic girdle muscle weakness, hyporeflexia and prominent calves.
Question 2 Continued

The sign demonstrated is:
A. Heimlich maneuver
B. Gower maneuver
C. Meryon maneuver
D. Duchenne maneuver

Question 3

The most likely diagnosis is:
A. Limb girdle muscular dystrophy
B. Congenital muscular dystrophy
C. Duchenne muscular dystrophy
D. Nemaline rod myopathy
Question 4
What causes the typical “waddle” or myopathic gait seen in Duchenne muscular dystrophy?
A. Hip and knee extensor weakness
B. Hip flexion and ankle plantar flexion contractures
C. Hip extensor weakness and knee flexor weakness
D. Hip and knee flexor weakness

Question 5
What is the pathophysiology of Duchenne muscular dystrophy?
A. Merosin deficiency
B. Abnormally low levels of dysferlin
C. Absence of dystrophin
D. Loss of alpha-dystroglycan

Question 6
The single most definitive test to make the diagnosis is:
A. Creatine kinase
B. EMG
C. DMD/BMD gene deletion studies
D. Muscle biopsy
### Table: Duchenne vs. Becker

<table>
<thead>
<tr>
<th>Incidence</th>
<th>1:3,500 live male births</th>
<th>1:30,000 live male births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of presentation</td>
<td>3-5 yrs</td>
<td>5-10 yrs, sometimes adolescence</td>
</tr>
<tr>
<td>Loss of ambulation</td>
<td>Before 13th birthday</td>
<td>Beyond 16th birthday</td>
</tr>
<tr>
<td>Death</td>
<td>Early 20's - from cardiac pulmonary failure</td>
<td>Variable - long term survival possible</td>
</tr>
<tr>
<td>CK</td>
<td>Massively elevated &gt; 10-100 X normal</td>
<td>Massively elevated &gt; 10-100 X normal</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Late – end stage</td>
<td>Early, disproportionate to muscle weakness</td>
</tr>
<tr>
<td>Dystrophin</td>
<td>Absent (&lt; 5%)</td>
<td>Reduced in quantity or quality &gt; 10%</td>
</tr>
<tr>
<td>Gene deletion</td>
<td>About 2/3 of cases</td>
<td>About 2/3 of cases</td>
</tr>
</tbody>
</table>

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### Question 7

The risk for a daughter of a female carrier of Becker muscular dystrophy being a carrier is:

A. 25%
B. 50%
C. 75%
D. 100%
E. No risk

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Adapted from Bönneman et al. Current Opinion in Pediatrics 1996; 8: 569 – 582

Neuromuscular Disorders | Peds Review Course 2012

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Image credits: [Adapted from Bönneman et al.](#)
DMD Gene

- Mutations
  - 65% involve large scale deletions
  - 5% involve duplications
  - 30% due to point mutations or small deletions
  - Mutations predict phenotype on most cases
- Mother identified as carriers in 2/3 of cases
  - Spontaneous mutations (1 in 10,000 gametes)
  - Germline mosaicism
  - 5-10% of female carriers manifest signs
  - Variable clinical presentation – remember cardiomyopathy!

Duchenne/Becker Muscular Dystrophy

- Complications
  - Respiratory failure, nocturnal hypoventilation
  - Cardiac failure, cardiomyopathy in BMD (fibrosis of posterobasal LV wall)
  - Contractures, scoliosis
  - Cognitive deficits – 1 S.D. Below mean, non progressive
  - Autistic-like features (exon 45 deletion)
Limb Girdle Muscular Dystrophy

- Clinically and genetically heterogeneous group of conditions
- Initially a diagnosis of exclusion
- Molecular genetics and protein identification has resulted in:
  - Increased understanding of pathophysiology
  - Improved classification, diagnosis, and prognostication
  - Better clinical characterization of these disorders

### Classification

**Autosomal Dominant**
- LGMD1A 5q31 Myotilin
- LGMD1B 1q21.2 Lamin A/C
- LGMD1C 3p25 Caveolin
- LGMD1D 7q Not known

**Autosomal Recessive**
- LGMD2A 15q Calpain
- LGMD2B 2p13 Dysferlin
- LGMD2C 13q12 γ-sarcoglycan
- LGMD2D 17q12 α-sarcoglycan
- LGMD2E 4q12 β-sarcoglycan
- LGMD2F 5q33 δ-sarcoglycan
- LGMD2G 17q12 Telethonin
- LGMD2H 9q E3-ubiquitin ligase
- LGMD2I 19q13.3 Fukutin-related protein
- LGMD2J 2q24.3 Titin

*From Bönneman et al. Current Opinion in Pediatrics 1996; 8: 569 – 582*
LGMD2B
Dysferlin
**Sarcoglycanopathies** (LGMD 2C – 2F)

- Form a distinct sub-complex
- Loss of any of the subunits results in muscular dystrophy
- Crucial role in membrane integrity
- Dystrophin may be secondarily reduced


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**LGMD2C**

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**LGMD 2F**

Courtesy of Carsten Bonnemann
Question 8

The following are all features of Emery-Dreifuss muscular dystrophy EXCEPT:

- a. Contractures of elbows
- b. Cardiomyopathy
- c. Autosomal or X-linked genetic inheritance
- d. Onset in infancy

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 dominant forms
Emery-Dreifuss Muscular Dystrophy

Courtesy of Dr Susan Stugaitis

LMNA Gene

- On chromosome 1q21.3
- Codes for the gene product: lamin A and C
  - nuclear proteins (type V intermediate filaments)
- Mutations associated with:
  - AD-EDMD
  - LGMD 1B
  - Cardiomyopathy with conduction defect
  - CMD1A
  - Pure form of isolated dilated cardiomyopathy
  - Familial Partial Lipodystrophy C
  - CMT 2B1
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: 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%)
Congenital Muscular Dystrophy

- Clinically and genetically heterogenous
- Characteristic phenotype, but overlap between some entities
- Classification based on phenotype and primary or secondary protein defects
- At least 11 genes involved to date
  - 9 genes identified

### CMD Where Causative Gene Known

<table>
<thead>
<tr>
<th>Name</th>
<th>Brain Involvement</th>
<th>Gene Symbol</th>
<th>Location</th>
<th>Protein</th>
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<tbody>
<tr>
<td>Merosin deficient</td>
<td>White matter hypodensity</td>
<td>LAMA2</td>
<td>6q</td>
<td>Laminin-alpha2</td>
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<tr>
<td>Fukayama</td>
<td>Mental retardation and structural changes</td>
<td>FKTN</td>
<td>9q</td>
<td>Fukitin</td>
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<tr>
<td>Muscle-eye-brain disease</td>
<td>Structural changes</td>
<td>POMGnT1</td>
<td>1p</td>
<td>POMGnT1</td>
</tr>
<tr>
<td>Walker-Warburg syndrome</td>
<td>Structural changes</td>
<td>POMT1</td>
<td>9q</td>
<td>POMT1</td>
</tr>
<tr>
<td>MDC1C</td>
<td>Variable</td>
<td>FKRP</td>
<td>19</td>
<td>FKRP</td>
</tr>
<tr>
<td>MDC1D</td>
<td>Mental retardation and structural changes</td>
<td>LARGE</td>
<td>22q</td>
<td>LARGE</td>
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<tr>
<td>RSMD1</td>
<td>None</td>
<td>SEPN1</td>
<td>1p</td>
<td>Selenoprotein-1</td>
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<tr>
<td>Integrin at deficiency</td>
<td>None</td>
<td>ITGA7</td>
<td>12q</td>
<td>Integrin alpha7</td>
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<tr>
<td>Ullrich disease</td>
<td>None</td>
<td>COL6A1, A2, A3</td>
<td>2 and 21q</td>
<td>Collagen VI</td>
</tr>
</tbody>
</table>

### Clinical Presentation

- **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 may occur (CMD +)
  - CK – variable (normal to very high)
Congenital Muscular Dystrophy
Merosin -

Ullrich Myopathy

Ullrich muscular dystrophy
Do not Confuse !!

• Congenital muscular dystrophy
• Myotonia congenita
• Congenital myotonic dystrophy
Questions?