Overview of Duchenne and Becker MD

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Roadmap

**Topics**
- Causes of DMD & BMD
- Consequences
- Care Considerations
- Cure

**Process**
- Identify the problems
- Innovation in science
- Investigation: therapy
- Improvement in care
Dystrophinopathies

- Classic Duchenne phenotype
- Becker phenotype
- Cardiac phenotype
- Exercise – Myalgias phenotype

Dystrophinopathies
Duchenne muscular dystrophy

- 1:3,500 boys
- Onset 2-4 years
  - delayed motor milestones: 42%
  - Abnormal gait: 30%
  - Speech delay and LD: 30%
- Proximal > Distal weakness
- Large Calves
- Wheelchair < 12 yrs
- Lifespan into 3rd decade
- Death from cardiac and respiratory failure
Duchenne Muscular Dystrophy Timeline

<table>
<thead>
<tr>
<th>YEARS</th>
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<tbody>
<tr>
<td>AGE</td>
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<table>
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<tr>
<th>STAGE</th>
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<tbody>
<tr>
<td>Pre-symptomatic Diagnosis</td>
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<tr>
<td>Making slow gains Plateau</td>
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<tr>
<td>Regression in leg function</td>
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<tr>
<td>Loss of ambulation by age 12</td>
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<tr>
<td>Regression in arm function</td>
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<tr>
<td>Spinal curvature Pulmonary Decline</td>
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<td>Cardiac Decline Death</td>
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Management Issues

• Steroid Treatment
• Physical Therapy: contractures, mobility
• Nutrition: avoid obesity
• Annual influenza immunization
• Special educational needs
• Monitor and Treat:
  – Scoliosis → Orthopedic evaluation
  – Heart Failure
  – Decreased lung function, sleep apnea
Becker muscular dystrophy

- 1: 12,000 males
- Onset and course variable
- Proximal > Distal weakness
  - may be limited to quads
  - exercise-induced myalgias
  - walk for 15+ years on average
  - wheelchair > 16 yrs
  - lifespan variable (average = 40s)
  - death from heart failure
Genetic Basis of DMD & BMD

**Gene mutation** = error in DNA sequence
- DMD and BMD in **dystrophin gene**
- X-chromosome location; boys affected
- All ethnic groups
- 2/3 of mothers are “carriers”
- Location and type of mutation are important
Genetic Structure
The Dystrophin Gene

From: Aartsma-Rus et al, Muscle and Nerve, 2006; 34:135-144
• Boy with clinical features, elevated CK, (EMG+)
• **Molecular Genetic Testing** confirms dystrophin disorder
  – Duchenne: predicted by “nonsense” mutation (93%)
  – Becker: predicted by a “missense” mutation (98%)
  – Carrier testing: can be done in commercial labs now
• Multi-step DNA analysis
  – Look for big deletion 1st
  – Then look for small deletion, duplications, point mutations
• 2007: new gene chip for diagnosis available
Chemical Level

DNA

RNA

Amino acids

Protein
Abnormal Dystrophin Protein

• Gene mutation affects amino acid synthesis
• Results in abnormal dystrophin protein
  – Absent/unstable protein = DMD
  – Reduced amount = BMD
  – Shorter but stable protein = BMD
• Affects cell function
  – Mechanical stress
  – Signaling of complex processes in cell
  – Calcium accumulation in cell
Dystrophin DNA Mutations

- Entire gene deleted = rare
- Large mutation in the gene (spans 1+ exon)
  - deletion (72%, Leiden), “hot spot” at exons 44-53
  - duplication (7%), “hot spot” at exons 2-20
- Small scale change (< 1 exon) = 20%
  - Deletion
  - Insertion
  - Point mutation (13% are “premature stop”)

*Important to genotype every DMD & BMD boy*
Muscle Biopsy: dystrophic changes

Normal

Duchenne
Location of Dystrophin Protein

protein complex at edge of muscle fiber

Dystrophin

contractile elements
Immunohistochemistry and Western blot

**Duchenne:**
absent (<2%) dystrophin

**Becker:**
reduced amount of smaller protein

**Carrier female:**
half muscle fibers with absent dystrophin

**Western Blot:** band indicates amount and weight of dystrophin
A VICIOUS CYCLE

Lack of dystrophin → Calcium influx → Activation of enzymes → Inflammation & Cell death → Muscle replacement

Scarring
DYSTROPHIN DEFICIENT MUSCLE

Dystrophin-glycoprotein complex affected
Decreased membrane stability

Calcium influx

Mechanical activity

Membrane damage
Activation of proteases

Calcium overload

Secondary changes:
Altered gene transcription, Enzyme activation
Mitochondrial damage, Myofibril damage
Cell signalling disruption, Oxidative damage

Necrosis
Apoptosis

Inflammatory response
Mononuclear cell infiltration
Fibrosis
Organs

- Muscles
- Bones
- Heart
- Blood vessels
- Lungs
- Brain
- Gastrointestinal Tract
Thank You

- PPMD
- Patients and Parents