Duchenne Muscular Dystrophy: Utilizing Personalized Treatments and Addressing Health Disparities

ANN TILTON, MD
PROFESSOR OF NEUROLOGY AND PEDIATRIC
LSU HEALTH SCIENCES CENTER - NEW ORLEANS

Learning Objectives

• Describe Duchenne Muscular Dystrophy (DMD) and the interprofessional care that is necessary for optimal outcomes.
• Explain different emerging therapies and how to incorporate these considerations into a personalized treatment plan.
• Discuss the prevalence of DMD in different racial and ethnic groups.
• Address health disparities among individuals with DMD related to their socioeconomic status, residential geographic location and access to DMD centers.
• Recognize other environmental factors that impact outcomes for individuals with DMD.
Case Studies

- John is a 10 yr old with progressive weakness first noted at 3 yrs when he had stumbling

Parents report:
- Difficulty with stairs and rising from the floor
- Toe walking
- Pain in his calves
- School difficulties

What do you consider?
Progressive Dystrophies

- Dystrophinopathies
  - Duchenne Muscular Dystrophy (DMD)
    - 1 in 3300 live male births
    - Spontaneous mutation rate of 1 in 10,000
    - Significantly more prominent in white males
      - Black and Hispanic males were evaluated later
      - Implications for therapy and outcome
      - The personalized care is impacted
  - Becker’s Muscular Dystrophy (BMD)
    - 1 in 31,000 male births

Historical Background

- 1980 mapping led to the gene Xp21
- 1985 microscopic observable deletion at Xp21
Duchenne Muscular Dystrophy: Utilizing Personalized Treatments and Addressing Health

**Dystrophinopathies**

- DMD gene is the largest gene identified in humans
- 1% of the entire X chromosome
- Protein product was named Dystrophin

**Dystrophinopathies**

- The DMD gene’s product is dystrophin
  - Dystrophin is part of a protein complex

Figure from Up to date
Duchenne Muscular Dystrophy: Utilizing Personalized Treatments and Addressing Health

**Dystrophinopathies**

- **Dystrophin**
  - Mechanical stabilization of the plasma membrane
  - Dystrophin may allow the membrane to fold during contraction-relaxation

**Diagnostics**

- Creatine kinase is dramatically elevated
  - 20-200 x normal
  - Max at 3yr and drops 20% per year
- EMG/NCV
- Elevated AST and ALT
- Gene test
- Muscle biopsy
Duchenne Muscular Dystrophy: Utilizing Personalized Treatments and Addressing Health

Diagnostics

- Muscle biopsy — Dystrophin
- Western blot
  - Quantitate the amount of dystrophin

Clinical Presentation

- Duchenne Muscular Dystrophy
  - < 2 years gross motor delay
    - Mean age walking is 18 months
  - Clinically apparent at 3-4 years of age
    - Proximal weakness
    - Calf hypertrophy
      - (pseudo-hypertrophy)
Duchenne Muscular Dystrophy: Utilizing Personalized Treatments and Addressing Health

Clinical Presentation

- Proximal weakness
  - Anterior pelvic tilt
  - Lumbar lordosis
  - Pelvic girdle first

- Myopathic gait pattern
  - Trendelenburg

Clinical Presentation

- Neck flexor weakness
- Gowers’ sign
Clinical Presentation

- Neck flexor weakness
- Gower's sign
- 25% intellectually disabled
- Progressive deterioration

Clinical Presentation

- Motor System
  - Honeymoon phase 3-6 yrs (50% loss)
  - 6-13 yrs linear loss...
    levels again 14-15 yrs
Clinical Presentation

► Motor System
  ► What predicts loss of ambulation?
    ▶ If 12 sec or greater to walk 30 feet, then ambulation will be lost in 1 yr
  ► Wheelchair use?
    ▶ Untreated 7-13 yrs (10yr)
    ▶ >14 yrs consider BMD (or LGMD)

Clinical Presentation

► Progressive Disorder
  ► Scoliosis
    ▶ Prevalence varies 33-100%
    ▶ Correlates with age
      ▶ 50% by 15yr
      ▶ Progresses 11 to 42 degrees/yr
  ► Scoliosis is not caused by wheelchair use
    ▶ Both age and weakness related
Clinical Presentation

- Main distinction between DMD and BMD
  - Wheelchair dependency <12 years and >16 years

Symptom Management

- Progressive Disorder
  - Cardiac problems
    - 90% of patients abnormal EKG
    - Cardiomyopathy
      - 1/3 by 14 yrs and all >18 yrs
      - Echo-Left Ventricle
      - Milder forms-transplant
      - Cardiology Management
        - ACE inhibitors
Symptom Management

- Orthopedics
  - Stretching
  - AFO
  - Exercise
  - Scoliosis

Symptom Management

- Respiratory compromise
  - Questions
    - How do you sleep? Nightmares?
    - Headache? Day time sleepiness?
  - Pulmonary Colleagues
    - FVC 1-2x/yr
    - Non-invasive measures
    - Negative and positive pressure
Symptom Management

- GI (smooth muscle)
  - Intestinal hypo-motility
  - Obesity then malnutrition
- Osteoporosis
  - Abnormal while still ambulatory
  - Calcium and Vitamin D
  - IV bisphosphonates
  - DEXA
- Anesthesia reaction

Symptom Management

- Complex Care
  - Multiple systems involved
  - Social impact?
    - Cognitive deficits
    - Psychosocial factors such as anxiety or depression
    - Physical limitations and fatigue
  - Environmental barriers
  - Disparities based on ethnicity and socioeconomic status
    - This is predominantly Muscular Dystrophy Association (MDA) center based so access is an issue
Symptom Management

- Complex Care
  - Multidisciplinary Approach is needed
    - GOALS
      - Strength and function
      - Prevention and treatment of spinal deformity
      - Addressing of respiratory and cardiac needs
      - Optimal outpatient and home-based management
      - Improved quality of life and reduced:
        - Emergency care and hospitalizations
    - Transition of Care
      - Difficult in children with complex medical issues
      - MDA system (but availability issues)

Therapeutics

- Weakness and a role for exercise?
  - Recommend:
    - Submaximal low impact aerobic exercise
    - Not to cramping or exhaustion
  - Benefits
    - 20% increase in strength
    - Endurance
    - Fatigue
    - Well-being
Duchenne Muscular Dystrophy: Utilizing Personalized Treatments and Addressing Health

November 30, 2021

Therapeutics

- Glucocorticoids-Mainstay
  - Offer at 4 yrs and older
  - Prednisone (and deflazacort)
    - Strength increase 11% and maintained (10 days)
    - Independent ambulation 3.3 yrs longer
  - FVC improved
  - Reduces heart failure
  - Scoliosis risk 20% vs 92%
  - Remember side effects

Therapeutics

- Exercise
- Steroids
- Novel Therapies
  - Exon skipping
  - Gene therapy
  - Viral vectors
  - Myostatin inactivation
  - Myoblast transfer
  - Immune suppressants
Therapeutics

- **Novel Therapies**
  - Exon skipping
  - Gene Therapy
    - Viral Vectors
  - Myostatin inactivation
  - Myoblast Transfer
  - Immune suppressants

Therapeutics

- **Novel Therapies**
  - **Exon skipping**
    - Designed to increase the production of dystrophin
    - It is not certain that it results in clinical benefit
  - Include:
    - Eteplirsen (exon 51)-13%
    - Golodirsen (exon 53)-8%
    - Vilofencsen (exon 53)-8%
    - Casimersen (exon 45)-8%
  - Skip over part of the genetic code - exon
  - Allows the production of a shorter but functional dystrophin protein
Duchenne Muscular Dystrophy: Utilizing Personalized Treatments and Addressing Health

November 30, 2021

Dr. Ann Tilton

---

**Therapeutics**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Exon Mutation</th>
<th>Ages</th>
<th>Delivery</th>
<th>Frequency</th>
<th>Cost per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exondys (Eteplirsen)</td>
<td>51</td>
<td>all</td>
<td>IV</td>
<td>Weekly</td>
<td>750,000</td>
</tr>
<tr>
<td>Vyondys (Golodirsen)</td>
<td>53</td>
<td>all</td>
<td>IV</td>
<td>Weekly</td>
<td>300,000</td>
</tr>
<tr>
<td>Viltelpso (Viltolarsen)</td>
<td>53</td>
<td>all</td>
<td>IV</td>
<td>Weekly</td>
<td>730,000</td>
</tr>
<tr>
<td>Amondys (Casimersen)</td>
<td>45</td>
<td>all</td>
<td>IV</td>
<td>Weekly</td>
<td>750,000</td>
</tr>
<tr>
<td>Emlaza (Deflazacort)</td>
<td>2 year plus</td>
<td>Oral</td>
<td>Daily</td>
<td></td>
<td>82,000</td>
</tr>
</tbody>
</table>

---

Exondys 51

Exon Skipping: Dystrophin Splicing With Exondys 51

---

Dr. Ann Tilton
Duchenne Muscular Dystrophy: Utilizing Personalized Treatments and Addressing Health

Stop codon
- Ataluren, Eteplirsen
  - Up to 15% of patients have a premature stop codon
  - Created by a nonsense mutation
  - Able to bypass the mutation and continue the translation codon
  - Functional protein

- Trial of 174 males – high, low and placebo
  - Low dose improved walking

Conclusion
There are more possibilities and many reasons for greater optimism