Duchenne Muscular Dystrophy:
Utilizing Personalized Treatments and Addressing Health Disparities

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

1

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.

2

Case Studies

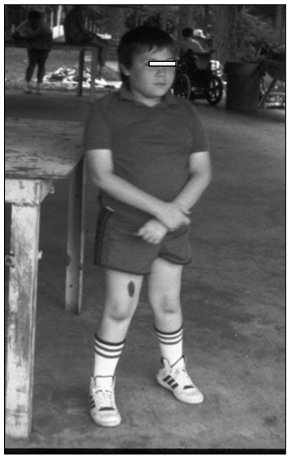
- John is a 10 yr old with progressive weakness first noted at 3 yrs when he had stumbling

3

Case Studies

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

What do you consider?



4

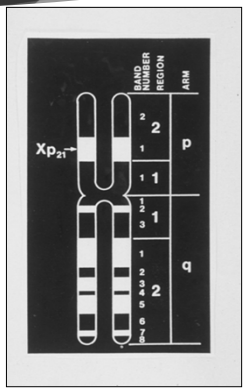
Progressive Dystrophies

- 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

5

Historical Background

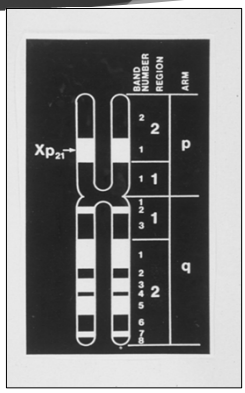
- 1980 mapping led to the gene Xp21
- 1985 microscopic observable deletion at Xp21



6

Dystrophinopathies

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



7

Dystrophinopathies

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

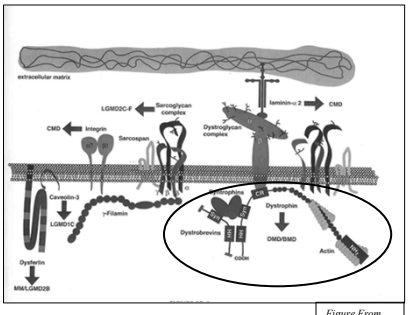


Figure From Up to date

8

Dystrophinopathies

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

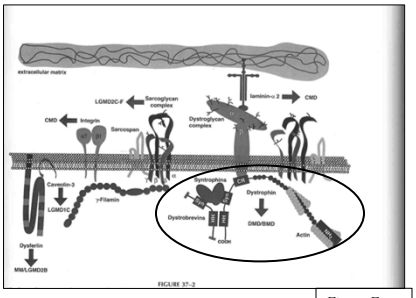
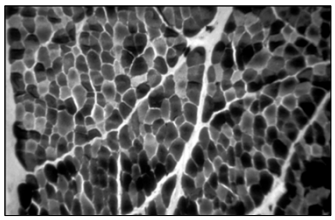


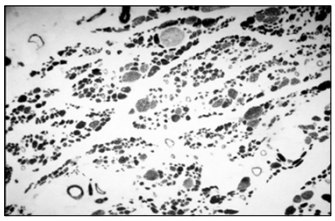
Figure From Up to date

9

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

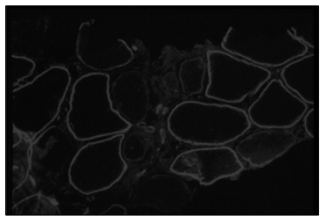


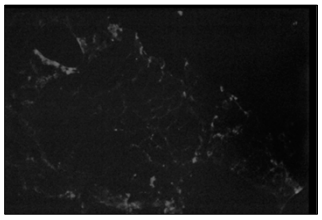


10

Diagnostics

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





11

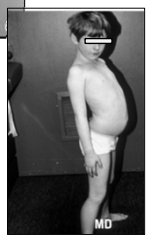
Clinical Presentation

- 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)

12

Clinical Presentation

- Proximal weakness
  - Anterior pelvic tilt
  - Lumbar lordosis
  - Pelvic girdle first
- Myopathic gait pattern
  - Trendelenburg

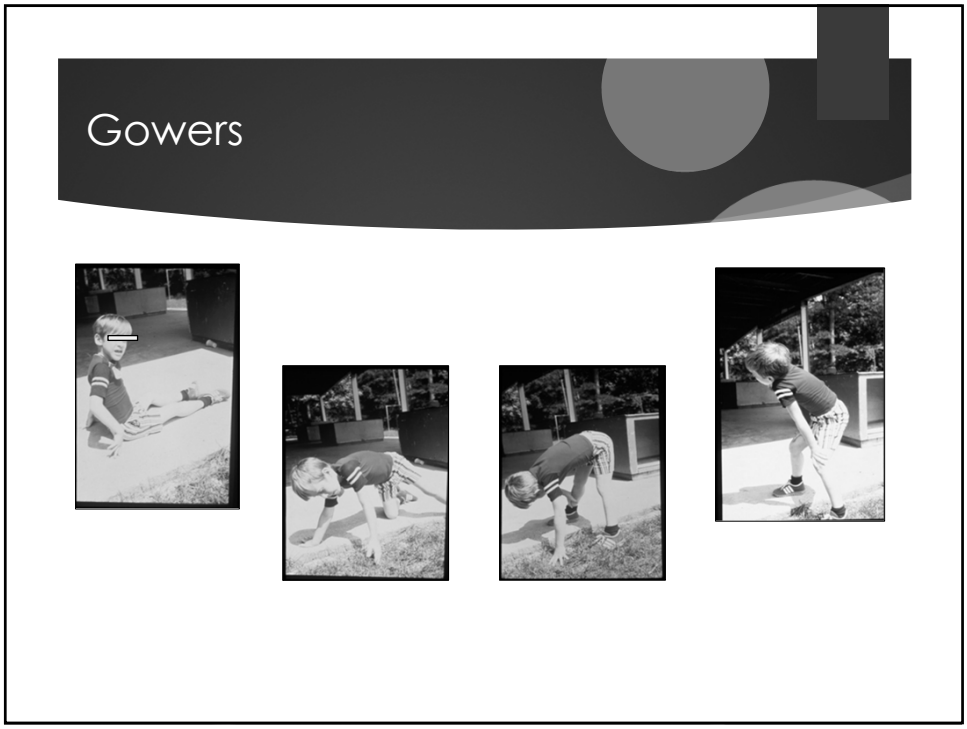


13

Clinical Presentation

- Neck flexor weakness
- Gowers' sign

14



15

16

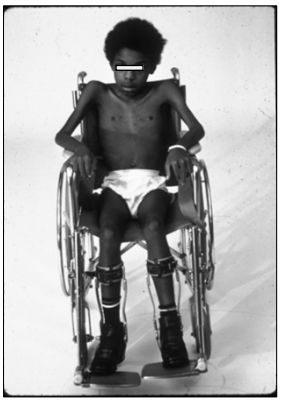
Clinical Presentation

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

17

Clinical Presentation

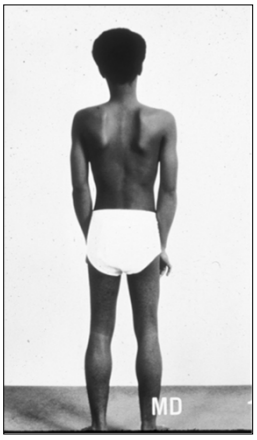
- Motor System
  - Honeymoon phase 3-6 yrs (50% loss)
  - 6-13 yrs linear loss… levels again 14-15 yrs



18

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)



19

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

20

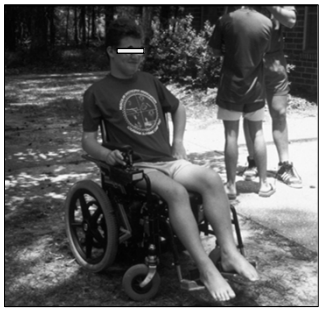
Clinical Presentation

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

21

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



22

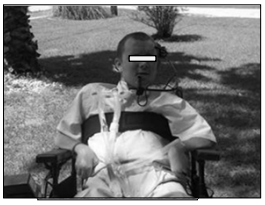
Symptom Management

- Orthopedics
  - Stretching
  - AFO
  - Exercise
  - Scoliosis

23

Symptom Management

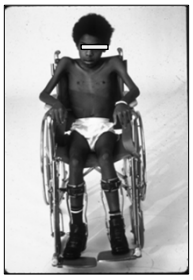
- Respiratory compromise
  - Questions
    - How do you sleep? Nightmares?
    - Headache? Day time sleepiness?
  - Pulmonary Colleagues
    - FVC 1-2x/yr
    - Non-invasive measures
    - Negative and positive pressure



24

Symptom Management

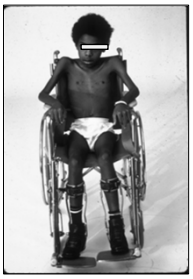
- GI (smooth muscle)
  - Intestinal hypo-motility
  - Obesity then malnutrition
- Osteoporosis
  - Abnormal while still ambulatory
    - Calcium and Vitamin D
    - IV bisphosphonates
    - DEXA
- Anesthesia reaction



25

Symptom Management

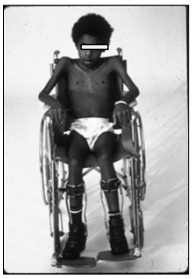
- Complex Care
  - Multiple systems involved
  - Social impact?
    - Cognitive deficits
    - Psychosocial factors such as anxiety or depression
    - Physical limitations and fatigue
  - Environmental barriers
  - Disparities based on ethnicity and socioeconomic status
    - This is predominantly Muscular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



26

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)



27

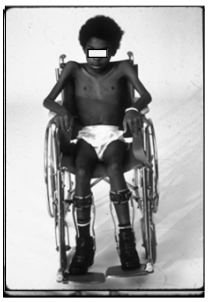
Therapeutics

- 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

28

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



29

Therapeutics

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

30

Therapeutics

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

31

Therapeutics

- Novel Therapies
  - **Exon skipping**
    - Designed to increase the production of dystrophin
    - It is not certain that it results in clinical benefit
  - Include:
    - Etepilirsen (exon 51)-13%
    - Golodirsen (exon 53)-8%
    - Vilolarsen (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

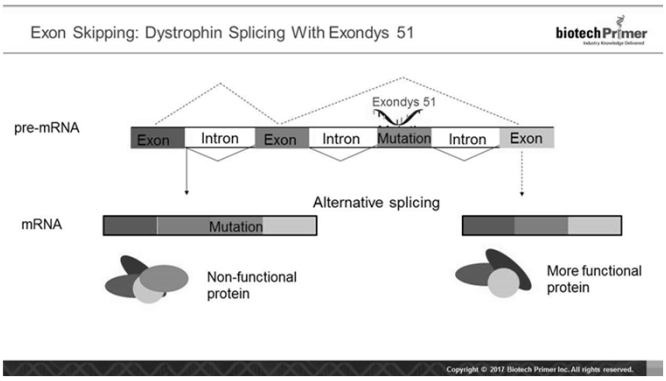
32

Therapeutics

Medication	Exon Mutation	Ages	Delivery	Frequency	Cost per year
Exondys *(Eteplirsen)*	51	all	IV	Weekly	750,000
Vyondys (Golodirsen)	53	all	IV	Weekly	300,000
Viltepso (Viltolarsen)	53	all	IV	Weekly	730,000
Amondys (Casimersen)	45	all	IV	Weekly	750,000
Emlaza (Deflazacort)		2 year plus	Oral	Daily	82,000

33

Exondys 51



34

Therapeutics

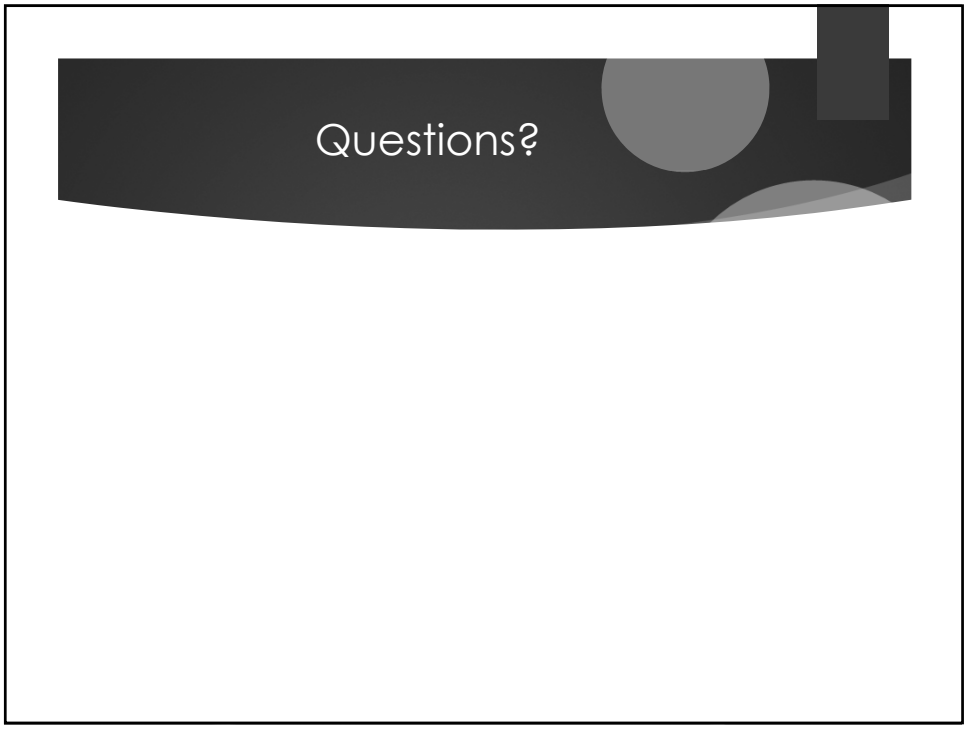
- Stop codon
  - Ataluren, Eteplirsen
    - Up to 15% of patients have a premature stop codon
    - Created by a nonsense mutation
    - Able to bypass the mutation and continue the translation codon 51,53 – functional protein
    - Trial of 174 males – high , low and placebo
      - Low dose improved walking

35

Conclusion

There are more possibilities and many reasons for greater optimism

36



37

38