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UPDATES IN DUCHENNE MUSCULAR DYSTROPHY

Learning Objectives

1. Become familiar with new therapeutic options for Duchenne muscular dystrophy

2. Identify which patients may be amenable for newer treatment options

Financial Disclosure

- I have no relevant financial disclosures

True Story

- A 3-year-old boy presents to the office for difficulty walking. His parents note that he frequently goes on his tiptoes, but think he is otherwise well. On examination, the patient makes poor eye contact with you, doesn't speak much and has enlarged calves. When getting up from a seated position, he has to climb up his legs. His uncle passed away from a degenerative condition. The obstetrician made sure that condition was not passed on.

Muscular dystrophy

Diseases of muscle

- Dystrophy – progressive and degenerative
- Myopathy – relatively static

Presentation

How might these kids come to you?

- Tip-toe walking
- Tripping, stumbling
- Trouble climbing stairs
- Easily fatigued
- Elevated AST/ALT

History

Specific questions relating to muscle function:

- Proximal strength: difficulty walking, difficulty reaching things higher up
- Distal strength: Difficulty with writing or holding objects, tripping or stumbling
- Facial strength: Smiling, wrinkling the forehead, extraocular movements
- Fatigability
- Exercise intolerance

History supplemental

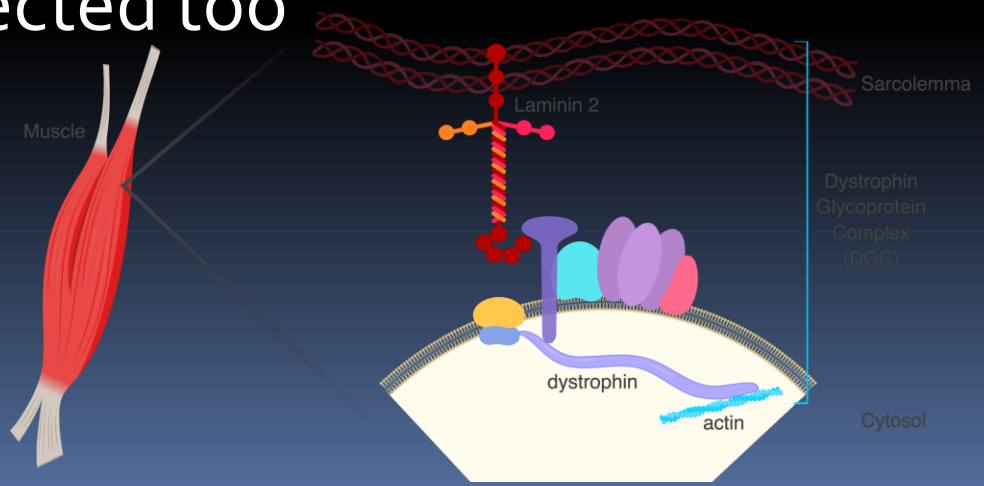
- Family history
  - Mothers or sisters with heart disease
  - Males with decline
- Developmental history
  - Difficulty with learning in school?
  - Difficulty with speech?
  - Difficulty keeping up with peers?
  - Attention problems?
  - Social-communications issues?

Physical examination

- Probably not going to get a formal muscle exam
  - Gower sign
  - Squat and stand, arms crossed
  - Stand up from a chair, arms crossed
  - Climb up a step, arms crossed
- Social evaluation
  - Gaze
  - Playfulness, reciprocity

Genetics

- X-linked recessive
- 1/3 new mutation
- rarely in girls with skewed inactivation
- Out-of-frame deletion → Duchenne
- In-frame deletion → Becker
- Carriers can be affected too

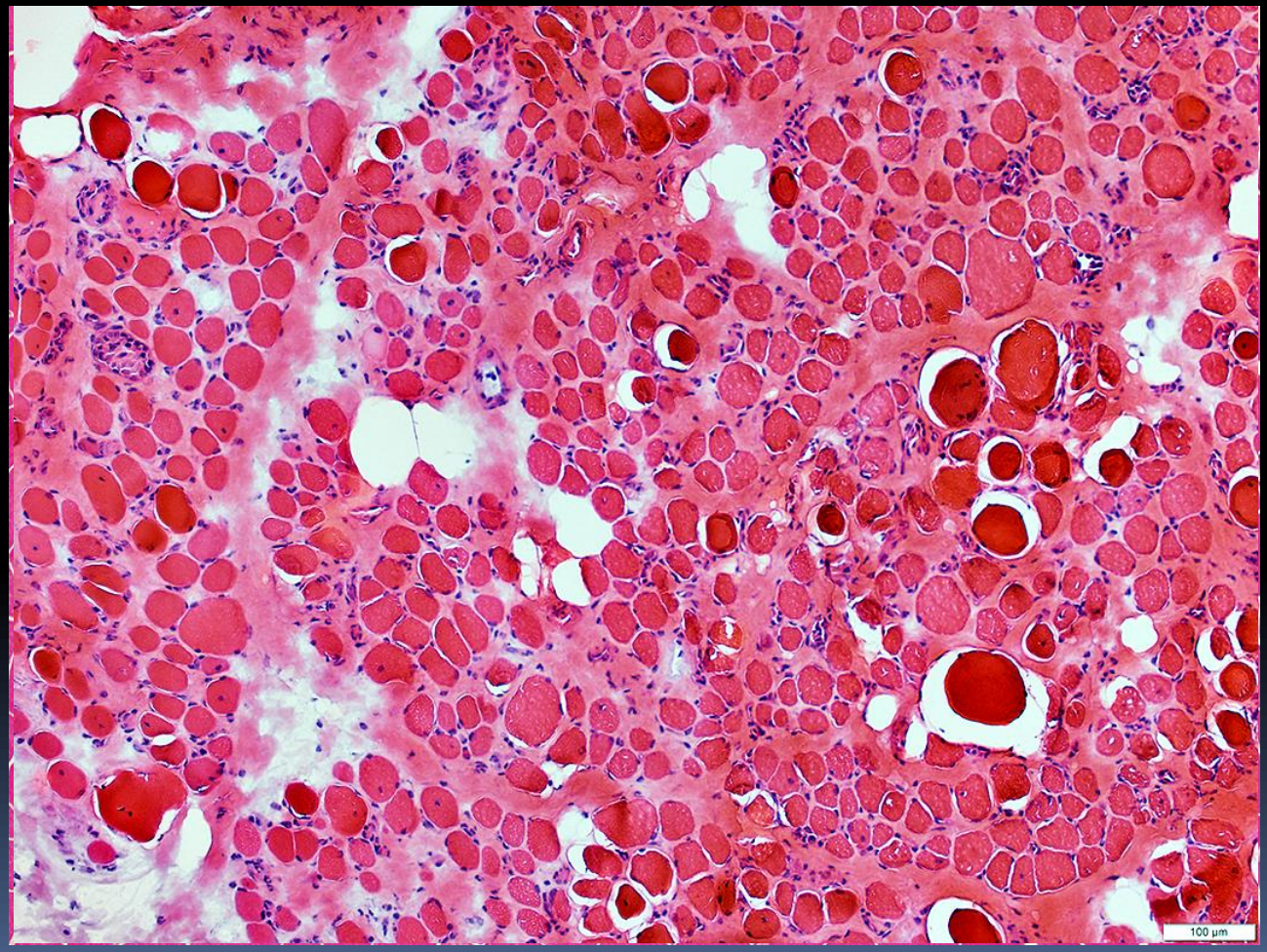


https://lab.research.sickkids.ca/cohn/projects/

What testing do we do?

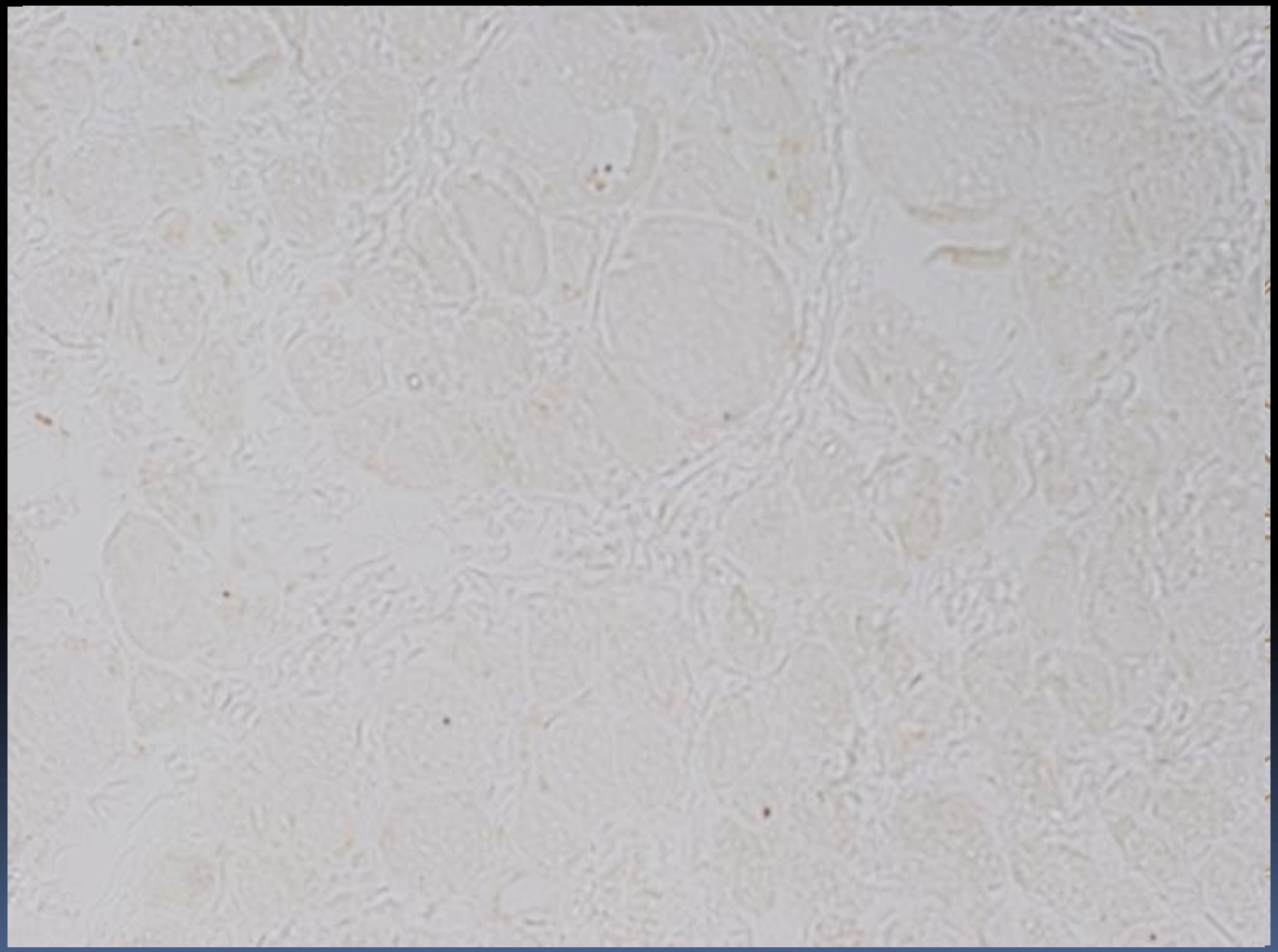
1. Serum	CK 10,000s
2. EMG/NCS	myopathic changes
3. Muscle biopsy	inflammation, decreased dystrophin staining
4. Genetic testing	deletion/mutation in Xp21 dystrophin gene

Muscle Biopsy H&E



https://neuromuscular.wustl.edu/pathol/dmdpath.htm

Muscle biopsy dystrophin



Management

Multidisciplinary care

- Genetics
- Annual ophthalmology visits
- Cardiology – especially teens, female family
- Pulmonology – especially teens
- Developmental Pediatrics
- Physiatry
- Orthopedics – scoliosis
- PT/OT/ST/DI +/- ABA

Pharmacologics - Steroids

- Oral prednisone/prednisolone – 0.75 mg/kg/day
- Deflazacort 0.9 mg/kg/day daily – less issues with weight gain
- Vamorolone 6 mg/kg/day – less bone issues
- 2-3 years more ambulation time
- Delayed scoliosis surgery
- Improved respiratory function
- Delayed cardiac deterioration

Givinostat

- First non-steroidal approved, March 2024
- 6 years old and up
- Histone deactylase inhibitor
- Promotes muscle formation, and reduces fibrosis and fatty replacement in muscle tissue
- Slows rates of decline in ambulation in studies
- Can use in combination with steroids and genetic therapies

Some additional basics first

- Largest known human gene – 79 exons, 2.3 mb length
- dystrophin comprises 0.002% of total muscle protein
- Large mutations in 79%, small in 21%
- Mostly clustered around exons 43 to 55
- Top five affected exons: 51, 53, 45, 43, 44
- AAV can carry 4.7 kb max

Eteplirsen

- Exon 51 skipping therapy, 2016
- Useful for 13-14% of DMD patients
- Morpholino – antisense oligonucleotide
- Once weekly 1-hour IV infusion for life
- Dystrophin production increased from 0.16% to 0.44% after 48 weeks
- Improvements seen with delayed ambulation loss, FVC decline

Golodirsen

- Exon 53 skipping therapy, 2019
- Useful for 8-10% of DMD patients
- Morpholino – antisense oligonucleotide
- Once weekly 1 hour IV infusion for life
- Dystrophin expression increased from 0.095% to 1.109% after 48 weeks
- No clinical benefit reported

Viltolarsen

- Exon 53 skipping therapy, since 2020
- Useful for 8-10% of DMD patients
- Morpholino – antisense oligonucleotide
- Once weekly 1 hour IV infusion for life
- Dystrophin protein production increased from 0.6 to 5.8% after 24 weeks in muscle biopsies
- Improvement on timed functional tests

Casimersen

- Exon 45 skipping therapy, since 2021
- Useful for 8-9% of DMD patients
- Morpholino – antisense oligonucleotide
- Once weekly 1-hour IV infusion for life
- Mean increase in dystrophin levels 0.81%
- Accelerated approval, study to complete this year
- No clinical benefit reported yet

Delandistrogene moxeparvovec-rokl

- Individuals 4 and up with DMD
- $3.2 million costs
- Single life time infusion
- Stored in -80° freezer, 14 days to infuse
- Adeno-associated virus vector – need to be Ab negative
- Can't have a deletion in exons 8 and 9
- Supplement additional steroids 60 days
- Weekly lab monitoring 90 days
- AE: myocarditis, liver, rhabdomyolysis, myositis

Further reading

- Evidence-based care in Duchenne muscular dystrophy. The Lancet, 2018
- Therapeutic Strategies for Duchenne Muscular Dystrophy: An Update. Genes, 2020