Muscular Dystrophy

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Case: William

- 5 year old boy
- Brought to pediatrician due to difficulty running
- Normal pregnancy and birth
- Walked at 16 months (late)
- Mom noticed William had large calves
- A brother had died of heart problems at age 12 (brother had similar calves)
Images of a 6-year-old boy with Duchenne muscular dystrophy showing calf hypertrophy evaluated from posterior view (A) and from lateral view, further accentuated by standing on toes (B).
Process of Medical Diagnosis

- Patient complaints: **Symptoms**
- Examination (physician’s observations): **Signs**
- Combination of above usually indicate which body system is affected:
  - Cough/sore throat: red throat on exam and swollen glands = upper respiratory system
  - Abdominal pain/diarrhea and tender belly on exam = gastrointestinal
When is a symptom due to problems with the nervous system?

- Problems with
  - Thinking/speaking
  - The senses: vision, touch, hearing
  - Movement/coordination
  - Autonomic (unconscious functions): bowel, bladder
Neurological Localization

- Where is the problem?
  - Brain
  - Spinal cord
  - Nerves
  - Muscle
Localization

- Where is the problem?
  - Brain
  - Spinal cord
  - Nerves
  - Muscle

Central nervous system

Peripheral Nervous system
CNS diseases

Epilepsy
Stroke
Multiple sclerosis
Migraine
Quadriplegia/paraplegia
Peripheral nervous system diseases

- Pinched nerves (carpal tunnel syndrome)
- Neuropathy (numb feet and hands)
- Myasthenia gravis (disconnection between nerve and muscle)
- Muscle disease
  - Muscular dystrophy
How can doctors tell if it is a disease of the CNS or PNS?

- If thinking is abnormal = brain
- If special senses (hearing/vision/taste/smell) are affected = brain or nerve to brain
- Reflexes help a lot:
  - Over-active reflexes = CNS
  - Under-active reflexes = PNS
William


- Eyes, hearing, speech, swallowing all normal.
- Only problem is “motor” so we are already thinking of a peripheral nervous system/muscle problem.
William’s Physical Examination

- Normal thinking and speech
- Normal eyes, ears, nose and mouth
- **Proximal** muscles are weak
  - Movement at the shoulders and elbows (biceps & triceps) weak
  - Movement at hips and knees weak
  - Wrists, hands and ankles are strong
- Normal sensation (touch, pinprick, etc)
- Reflexes are slightly reduced
- Waddling gait
- **POSITIVE GOWER’S MANEUVER**
Using hands to push on legs to stand

Gowers Sign

https://jamanetwork.com/journals/jama/fullarticle/1104723
Gowers Sign

A 5-year-old boy with Duchenne muscular dystrophy demonstrating the Gowers sign. Notice how he “climbs on himself” to stand up.
TESTING

ADDS DIAGNOSTIC CERTAINTY TO PHYSICIAN’S TENTATIVE DIAGNOSIS
CPK: CREATINE PHOSPHOKINASE

- Enzyme (protein that has important action in the body) which is abundant in muscle tissue.
- When muscle is damaged, CPK leaks out of muscle and into bloodstream.
- Diseases that damage muscle like muscular dystrophy cause increased levels.
- Elevated CPK is a good test to confirm if a patient has a muscle disease.
WILLIAM’S CPK

- 3,000 units/liter (normal is less than 200)
- Confirms the preliminary diagnosis of a muscle disease.
MUSCLE DISEASE

ISOLATED “PROXIMAL” WEAKNESS

ELEVATED CPK
WHICH MUSCLE DISEASE?

- HEREDITARY
- AQUIRED
  - MUSCLES ATTACKED BY IMMUNE SYSTEM
  - TOXIC SUBSTANCES
When serious diseases occur early in life (childhood) they are usually inherited (in the DNA).

INHERITED MUSCLE DISEASE = MUSCULAR DYSTROPHY
TYPES OF MUSCULAR DYSTROPHY

- GENDER
- AGE OF ONSET
- WEAKNESS PATTERN
- FAMILY HISTORY
- DEGREE OF CPK ELEVATION
Main areas of muscle weakness in different types of dystrophy:

- Duchenne and Becker Types
- Emery-Dreifuss Type
- Limb Girdle Type
- Facioscapulo-humeral Type
- Oculopharyngeal Type
Symptoms began before 5
Proximal weakness with normal facial muscles
Big calves
Family history?
  - Parents normal but mom has muscle pain
  - Older brother died at age 12 of unknown cardiac conditions
Very high CPK
Duchenne muscular dystrophy
Duchenne muscular dystrophy (DMD)

- Most common muscular dystrophy
- 1/3500-5000 boys
- Passed by mother on “X chromosome”
**X-LINKED RECESSIVE INHERITANCE**

- **Unaffected father**
- **Carrier mother**
- **Unaffected son**
- **Unaffected daughter**
- **Carrier daughter**
- **Affected son**

https://duchennecanada.org/disease-treatment/how-duchenne-is-inherited/
HOW TO DIAGNOSE MUSCULAR DYSTROPHY

- MUSCLE BIOPSY
- GENETIC TESTING
MUSCLE UNDER THE MICROSCOPE

NORMAL

DMD

https://neuromuscular.wustl.edu/pathol/dmdpath.htm#dmdolder
We can stain muscle samples with antibodies to dystrophin.

HOW TO DIAGNOSE MUSCULAR DYSTROPHY

- MUSCLE BIOPSY
- GENETIC TESTING
Genetic testing is now preferred

- Blood or saliva
- 100% sensitive and specific when the mutation is known
- Increasingly available through free programs
FIGURE 2-13

Subcellular localization of the limb-girdle muscular dystrophies.

FKRP = fukutin-related protein; LGMD = limb-girdle muscular dystrophy; POMT = protein-O-mannosyltransferase; DG = dystroglycan; POMGnT1 = protein-O-linked mannose β1, 2-N-acetylglucosaminyltransferase; SG = sarcoglycan; TRIM32 = tripartite motif containing protein 32.

Advancing DMD

- Loss of walking by age 12
- Progressive curvature of the spine
- Heart muscle becomes weak and electrical system misfires
- Breathing weakens
- Death usually occurs late 20s or early 30s.
Treatment: Steroids are beneficial in DMD

- Prolongs walking
- Prolong time free of ventilator
- Delays scoliosis
- Prolongs life

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Journal of the American College of Cardiology
Volume 61, Issue 9, March 2013
FDA News Release
FDA grants accelerated approval to first drug for Duchenne muscular dystrophy
For Immediate Release
September 19, 2016

The accelerated approval of Exondys 51 is based on the surrogate endpoint of dystrophin increase in skeletal muscle observed in some Exondys 51-treated patients.
How Exondys works:

Exon Skipping Therapy

NAME
Exondys 51 (Eteplirsen)

APPROVED FOR
Patients with Duchenne muscular dystrophy who have a confirmed mutation applicable to exon 51 skipping

TYPE
Phosphorodiamidate morpholino oligomer (PMO)

MOLECULAR TARGETS
RNA transcript of DMD, exon 51

CELLULAR TARGETS
Skeletal muscles expressing DMD transcript

EFFECTS ON TARGETS
Causes DMD transcript exon 51 to be skipped, putting the RNA back in frame and creating an internally deleted but somewhat functional dystrophin protein
Exondys: Exon-skipping therapy
Treatment

- Multidisciplinary care teams: MDA Care Center
  - Neurologist/Physical Medicine physician
  - Physical therapist
  - Occupational therapist
  - Social work
  - MDA coordinator
  - Genetic counselor
  - Pulmonary and cardiac physicians
  - Equipment (bracing, power chairs)
Future treatments

- Harmless virus to deliver missing gene
  - Preliminary results show success of this method in spinal muscular atrophy

- Stem cell treatments
How about other muscular dystrophies?

- Pompe disease: due to missing enzyme. Now treatment by replacing enzyme
- None are curable
- With success of viral vectors, search is underway for gene therapies for many types
Thank you!

Questions?