Duchenne muscular dystrophy (DMD)

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Pathology (Definition)

- Duchenne muscular dystrophy (DMD) is a genetic disorder affecting the largest gene in the human body
- progressive skeletal muscle degeneration (wasting) and weakness
- gene mutations result in alterations of *dystrophin* protein involved in keeping muscle cells intact
- Dystrophin connects cytoskeleton of individual muscle fibers to underlying basement lamina

> Absent dystrophin allows entry of excess Ca++

>> Ca++ triggers multiple signal pathways & allows movement of water into the cell

>>> Mitochondria burst

Pathogenesis/ Pathophysiology

- Etiology: mutation of dystrophin gene at locus Xp21 (short arm of the X chromosome)
- Mitochondrial dysfunction increases stress-responses
- Increased production of ROS
- Damage to sarcolemma leading to cell death (muscle fibres undergo necrosis.
- Necrosis is replaced with adipose + connective tissue

Epidemiology

- X-LINKED RECESSIVE
  typically males < 5years old ~ 1/3,500 worldwide
  female carriers (unaware until birth of affected son)

- extremely rare disease in females ~ 1/50,000,000
  Can occur in females with:
  1) affected father and carrier mother;
  2) in those who are missing an X chromosome;
  3) those who have inactivated X chromosome.

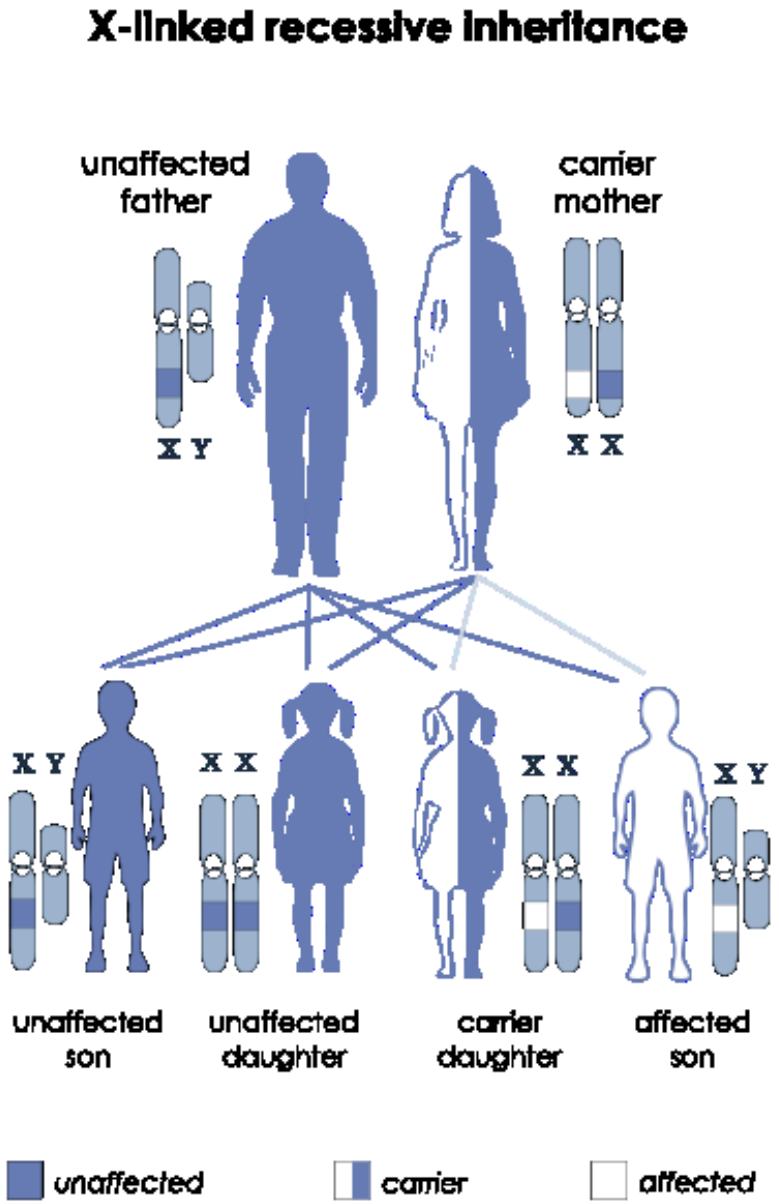
- 2010 US study – Hispanics most affected

Genetics

- Inherited – X-LINKED RECESSIVE DISEASE
- son of carrier mother has a 50% chance of inheriting defective gene
- daughter of carrier mother has 50% chance of being carrier AND 50% chance of having 2 normal copies of gene
- In all cases, unaffected father passes normal Y to son OR a normal X to his daughter
- Female carriers of X-linked recessive condition (e.g. DMD) can show symptoms depending on their pattern of X-inactivation (lyonization)

** (Mutations within the dystrophin gene can either be inherited or occur spontaneously during germline transmission??)*

X-Linked Inheretence



https://en.wikipedia.org/wiki/File:X-linked_recessive.svg

Signs & Symptoms

- Male infant, <5 years old – visible from first steps!
- Muscle wasting voluntary muscles affected first (hips/pelvic area & thighs/calves)
- progresses to the shoulders/neck, followed by arms/respiratory muscles…other…
- Fatigue
- Short Achilles' tendon
- Problems with motor skills (posture/gait – walk on toes)
- Trouble getting up from lying/sitting = Gower's Sign
- Spinal issues (lordosis/scoliosis)
- Cardiomyopathy (often dilated)
- Neurobehavioral/learning difficulties

Clinical Picture

POSITIVE GOWER'S SIGN

https://upload.wikimedia.org/wikipedia/commons/thumb/7/7c/Gower%27s_Sign.png/330px-Gower%27s_Sign.png

Drawing of 7-year-old boy with Duchenne muscular dystrophy. There is excessive development of the lower limbs (pseudohypertrophy), and thinness of the arms. In the figure on the right, lumbar hyperlordosis is visible.

https://upload.wikimedia.org/wikipedia/commons/thumb/4/49/Drawing_of_boy_with_Duchenne_muscular_dystrophy.png/330px-Drawing_of_boy_with_Duchenne_muscular_dystrophy.png

Diagnosis

- Genetic counselling for those with Familial Anamnesis OR carrier detection
- 95% accuracy of genetic studies during pregnancy (markers/genetic sequences)
- CVS @ 11 wks; Amniocentesis @ 15 weeks
- DNA test in affected patient – dystrophin gene mutation
- Muscle biopsy – immunohistochemistry, etc…

Treatment, Management & Prognosis

- No cure
- Av. life expectancy = 26 yrs (many living into 30s)
- Trx – aims to control onset of symptoms + optimal quality of life (use of questionaires)
- Corticosteroids (short-term improvements ~ 2 yrs)
- Physical Therapy
- Orthopaedics (braces/wheelchairs)
- Respiratory support
- Pacemaker for cardiac problems
- Eteplirsen: antisense oligo - controversially approved in US for trx of mutations due to dystrophin exon 51 skipping
- Ataluren: approved for certain cases in EU.
- Golodirsen: antisense oligo - approved in US in 2019 for the treatment of cases that benefit from skipping exon 53 of the dystrophin transcript