Duchenne is a multisystem disease

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Duchenne muscular dystrophy

X-linked recessive:
- 1/5000 male births

Common muscular dystrophy
- Resp/cardiac failure

Age (years) at death

Duchenne/Becker

All others
2.5mb DMD gene in 79 exons encodes dystrophin protein.
Duchenne can progress differently in different boys.

**Duchenne/Becker Genetic Modifier Study**

**LTBP4 Genotype Predicts Age of Ambulatory Loss in Duchenne Muscular Dystrophy**

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Objective: Duchenne muscular dystrophy (DMD) displays a clinical range that is not fully explained by the primary DMD mutations. LTBP4, encoding latent transforming growth factor-β binding protein 4, was previously discovered in a genome-wide scan as a modifier of mouse muscular dystrophy. We sought to determine whether LTBP4 genotypes influenced DMD severity in a large patient cohort.

Methods: Genomic DNA was isolated from 1627 consecutive muscle biopsy specimens from DMD patients. The distribution of LTBP4 genotypes was compared with respect to age of ambulatory loss (based on patient reports and medical records) in DMD patients with known DMD mutations. These included SMN deletion, V174L, T745A, T825A, and T1142M, four of the VTT and VAWUS haplotypes.

Results: Individuals homozygous for the VAWUS LTBP4 haplotype remained ambulatory significantly longer than those with heterozygous or homozygous for the VTT haplotype. Of 318 patients evaluated, 19 (6.0%) homozygous for VAWUS homozygous lost ambulation at 12.3 ± 3.3 years compared to 10.7 ± 2.1 years for those with VTT haplotypes. The L1142M variant was the strongest modifier, reducing the age of ambulatory loss by 2.5 years (95% CI, 0.5 to 4.5 years).

Interpretation: LTBP4 haplotypes influence age at loss of ambulation, and should be considered in the management of DMD patients.
DMD Mutation can predict dystrophin amount contribution to disease severity
Exceptions to reading frame rule

In frame mutations can be severe
Out of frame mutations can be mild
Exon 45 deletion can be more mild

HOT SPOT
In frame mutations can be severe
Variation in age at loss of ambulation from Duchenne Registry data
Muscle

• Lack of dystrophin at muscle cell membrane: leads to progressive damage to skeletal muscle
• High blood CK, High ALT/AST (so called liver function tests)
• Progressive weakness: Center of body weaker than distal
• Mild weakness > Loss of ability to rise from floor > Loss of ambulation > Loss of ability to transfer > Loss of ability to bring hands to mouth
• Contractures
  – Daily stretching/standing PWC/ROM exercise
• Mobility/Medical Equipment Needs
  – scooter > wheelchair

#PPMDCONFERENCE
Lungs

• Due to weak muscles of breathing
• Weak cough
  – Cough Assist
• Pneumonia
  – Antibiotics
  – Vaccines
• Chronic hypoventilation at night initially
  – BIPAP/AVAPS/Vent
Heart

- High lifetime risk of some degree of heart failure
- Arythmias
- Observable at younger ages with more sensitive heart measures
- Progressive
- Treatable
Bone

- Often low Vitamin D at diagnosis
- Steroids and less physical activity induce low bone mineral density>>Osteopenia/osteoporosis
  - Monitor/medications
- Fracture risk (about 40%)
  - Treatment depends on stage of disease
- Spinal Compression Fractures
- FAT EMBOLISM SYNDROME
- Scoliosis
  - Spinal fusion surgery
Endocrine

- Steroids: Adrenal insufficiency
  - Stress dosing/replacement/slow wean
- Steroids: Slowed growth
  - Growth hormone
- Steroids/Lack of mobility: Obesity
  - Diet/metformin
- Steroids: hyperglycemia
  - medications
- Delayed puberty
  - testosterone
Brain

• Some different forms of dystrophin expressed highly in brain cells
• Increased risk of affect on brain development, highly variable
  – Delayed speech
  – Social isolation
  – Rigidity
  – Easy frustration
• Learning disabilities in language and math
• Mild increase in seizure risk (?)
GI

- Nutritional Assessment
- Reflux
  - medications
- Swallowing difficulty
  - Modifications/G tube
- Chronic constipation
  - Stool softener; Maintain daily soft stools
- Bowel distension risk
- Toxic megacolon (atonic bowel/sepsis)
Takeaways
Duchenne has affects on many organs
Comprehensive care team needed
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