ABC’s of *Ryr1*-related Diseases

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Outline

• Diagnostic Process
  – Symptoms
  – EMG/NCV
  – Muscle MRI/ultrasound
  – Muscle Biopsy
  – Contracture Testing for MH
  – Genetic Testing

• Inheritance Patterns

• Genotype-Phenotype Correlations
Symptoms

- Long face
- Ptosis (drooping eye lids)
- Ophthalmoplegia (restricted movements of the eye muscles)
Symptoms (cont.)

- Muscle weakness
  - Facial and proximal (muscles closest to the core) muscles
  - Delays in sitting, walking, etc
  - Difficulties getting up off the floor/out of a chair
  - Difficulties walking
  - Difficulties with stairs

- Muscle wasting (muscles get smaller)

- Muscle cramping/pain

- Rhabdomyolysis (severe breakdown of muscle tissue, muscle cramping/pain/weakness, dark urine, high CK)

- Susceptibility to malignant hyperthermia (MH)
Symptoms (cont.)

- Contractures (fixed/stiff joints)
- Scoliosis (spine curvature)
- Changes in the shape of the chest
- Hip dislocation
Symptoms (cont.)

• Eating difficulties
• Breathing difficulties, sleep apnea (difficulties breathing during sleep)
• Fatigue (especially in warm weather), exercise intolerance
• Intelligence is typically normal
EMG/NCV

- Electromyography (EMG)
  - Assesses the muscle activity
  - Needle (recording microphone)

- Nerve conduction velocities (NCV)
  - Assesses the nerve signals
  - Recording electrodes placed over the nerves
Muscle MRI & Ultrasound

- Looks for patterns of muscle groups that are affected
Biopsy Findings of RYR1-related Myopathies

- Central Core Disease (CCD)
- Multiminicore Disease (MmD)
- Centronuclear Myopathy (CNM)
- Congenital Fiber Type Disproportion (CFTD)
- Nemaline Myopathy (NM)
- Congenital Muscular Dystrophy (CMD)
Contracture Testing

1) Equipment recording muscle contraction

Muscle Fiber

Electrical Stimulus

Baseline Muscle Contraction

2) Equipment recording muscle contraction

Muscle Fiber

Electrical Stimulus

+ Caffeine or Halothane

Normal Muscle Contraction (MH Negative)

Excessive Muscle Contraction (MH Positive)
Genetic Testing

- Options:
  - Sequencing
  - Deletion/Duplication
  - Panel
  - Whole exome/genome sequencing

- Interpretation of Results
  - Medical Literature
  - Prediction Programs
  - Prevalence of the Change
Autosomal Dominant Inheritance

- Central Core Disease
- Core-Rod Myopathy

1 in 2 chance that the child will be affected (50%)

1 in 2 chance that the child will not be affected (50%)
Autosomal Recessive Inheritance

- Central Core Disease
- Multiminicore Disease
- Centronuclear Myopathy
- Congenital Fiber Type Disproportion
- Nemaline Myopathy
- Core-Rod Myopathy
Genotype-Phenotype Correlations

• Location and type of the gene change
• Affect on protein levels
Central Core Disease

Core-Rod Myopathy

Core Myopathy

King Denborough Syndrome

Nemaline Myopathy

RYR1-Related Myopathy

Congenital Muscular Dystrophy

Multimincore Disease

Centronuclear Myopathy

Central Core Disease
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