Recent Advances in Neurology 2014: Neuromuscular Case Presentations

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Patient #1: Young woman with severe polyneuropathy

- 25 year-old woman
  - Normal motor and cognitive development
  - Short stature
  - At age 18, became amenorrheic
  - At age 18 or 19, developed steppage gait and numbness in the lower extremities
  - EMG/NCS – severe axonal polyneuropathy
  - At age 24, developed memory and word finding problems, though still able to work
  - Multiple hospitalizations for worsened weakness
    - Lactic acidosis
    - Chronic thrombocytopenia
    - Macrocytic anemia
    - Developed diabetes
    - Cirrhosis

Case History #2

- Family History
  - No neurodegenerative disorders
  - Parents are second cousins
- Exam
  - Enlarged liver
  - Cranial Nerves—normal including fundoscopic
  - Normal muscle tone; striking atrophy and weakness of the hand and leg muscles
  - Reflexes absent/hypoactive
  - Sensory examination—stocking distribution impairments of vibration and pain sensation
  - HKS- Clumsy; Wide-based, unsteady gait
- Labs
  - CK—Normal
  - INR 1.8
  - Hb 9.5 g.dL and MCV 105 fL (ULN < 100 fL)
  - Normal B12
  - Plasma lactate—Elevated

MR brain

T2 weighted, axial image. Confluent and symmetrical hyperintensities in deep and subcortical white matter of posterior frontal and parietal lobes, involving the subcortical U-fibers. There was no enhancement of these areas with gadolinium.
Leukoencephalopathy

Cirrhosis

Poly-neuropathy

Lactic Acidosis

Mitochondrial syndrome was suspected.

Which is true?

1. Each mitochondrion has multiple copies of mtDNA
2. mtDNA is double stranded and linear
3. mtDNA only replicates during cell division
4. Mitochondrial disorders are only inherited maternally

PLEASE SHOW RESPONSES!!

Mitochondrial DNA Depletion Syndromes

TESTING:
Hepatocerebral-DNA depletion syndrome panel:
Apparent homozygous mutations of MPV17

Mitochondrial DNA Depletion Syndromes

- Autosomal recessive
- Most syndromes present very early in life, but greater appreciation of adult-onset cases
- nDNA genes encode key proteins
  - Mitochondrial nucleotide synthesis
  - mtDNA replication
- nDNA mutations
  - Cause depletion (reduced copy number) of mtDNA
  - May also cause multiple mtDNA deletions
### Mitochondrial DNA Depletion Syndromes

<table>
<thead>
<tr>
<th>Mitochondrial Depletion Syndrome Phenotype</th>
<th>Gene(s)</th>
<th>Typical Age of Onset</th>
<th>Common Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopathic</td>
<td>TK2</td>
<td>Infancy or early childhood</td>
<td>Muscle weakness, hypotonia, bulbar weakness, elevated CK</td>
</tr>
<tr>
<td>Encephalomyopathic</td>
<td>SUCLA2, SUCLG1, RRM2B</td>
<td>Neonatal-Infancy</td>
<td>Hypotonia and muscle weakness, psychomotor delay, short stature, lactic acidosis, epilepsy</td>
</tr>
<tr>
<td>Haplophic</td>
<td>DGUOK, MPV17, POLG, C10orf2 (Twinkle)</td>
<td>Neonatal-childhood</td>
<td>Hepatic dysfunction, psychomotor delay, hypotonia, neuropathy, ataxia, lactic acidosis, stroke or stroke-like episodes, myoclonus and choreoathetosis, epilepsy, leukoencephalopathy, hearing loss</td>
</tr>
<tr>
<td>Neurogastrointestinal</td>
<td>TYMP</td>
<td>Late childhood-adolescence</td>
<td>GI dysmotility, weight loss, neuropathy, piosis, ophthalmoplegia, elevated thymidine and deoxyuridine in plasma, leukoencephalopathy</td>
</tr>
</tbody>
</table>

### MPV17 Mitochondrial DNA Depletion Syndrome

- Autosomal recessive
- Function of MPV17 is not known
- In addition to mtDNA depletion, patients accrue multiple mtDNA deletions
- Clinical:
  - Severe axonal, mixed fiber polyneuropathies
  - Liver: Steatohepatitis, cholestasis, cirrhosis and liver failure
  - Lactic acidosis
  - Leukoencephalopathy: Disabling cognitive problems and upper motor neuron signs not common
  - Novel in this case: Amenorrhea

### Mutations in the nuclear DNA may cause?

1. Reduced amounts of mtDNA in tissues
2. Multiple mtDNA deletions
3. Abnormalities on respiratory chain enzyme testing
4. All of the above

### Mitochondrial DNA depletion syndromes:

1. Are autosomal recessive
2. Usually present in infancy or early childhood
3. May have different phenotypes at different ages of presentation
4. All of the above
Patient #2: Myotonia congenita…or something else?

- 25-year-old man
  - Lifelong muscle pain
  - Exercise was pain-limited since childhood
  - No bouts of visible myoglobinuria; no muscle contractures

- Family history: Mother and Maternal GF -- similar symptoms; MGF US Army dx: congenital myotonia

- Exam:
  - Normal tone; normal or inc bulk; no grip myotonia
  - Percussion of muscles produced: Rapid contractions
    - Mounding of the muscles
    - Some rippling
  - Reflex, sensory, and gait examinations normal

- Testing: CK 693 U/L

Mutations of which of the following genes is **not** associated with myotonia?

1. **SCN4A** – sodium channel
2. **CACNA1S** – calcium channel
3. **CLCN1** – chloride channel
4. All of the above

Muscle Channelopathies

- **Chloride Channelopathies: Myotonia**
  - Myotonia Congenita
    - Autosomal Dominant – Thomsen disease
    - Autosomal Recessive – Becker disease

- **Sodium Channelopathies: Myotonia or Paralysis or Both**
  - Potassium-Aggravated Myotonia
  - Paramyotonia Congenita
  - Hyperkalemic Periodic Paralysis

- **Other Cation Channelopathies: Paralysis without Myotonia**
  - Calcium Channelopathy
    - Hypokalemic Periodic Paralysis (*some SCN4A)
  - Potassium Channelopathy
    - Andersen-Tawil syndrome
    - Thyrotoxic Periodic Paralysis
Myotonia: Electrodiagnostic Testing

TESTING: INCREASED INSERTIONAL ACTIVITY BUT NO MYOTONIA; NO DECREMENT OF CMAP ON REPEATED SHORT EXERCISE TESTING

Myotonia Congenita

- Symptoms: Stiffness; falls; difficulty letting go; warm-up phenomenon
- Onset: Early childhood
- Despite limitations, usually do well; can play some sports
- Exam: Muscle hypertrophy; clinical and EMG myotonia; Becker patients may have fixed weakness
- Caused by mutations of CLCN1
  - AD (Thomsen)
  - AR forms (Becker)
- AR > AD: Transient weakness shortly after initiating exercise

Could it be genetic rippling muscle disease?

Not again.

Caveolinopathies

- Caveolinopathies
  - CAV3-Related Distal Myopathy
  - CAV3-Related Hypertrophic Cardiomyopathy
  - CAV3-Related Isolated HyperCKemia
  - CAV3-Related Rippling Muscle Disease
  - Limb-Girdle Muscular Dystrophy Type 1C
- Patient TR: Mutation in CAV3
  - Arginine $\rightarrow$ Glutamine
Rippling Muscle Disease

Historical
- 1975: Torbergsen described a family with dominant hereditary “myotonia,” muscular hypertrophy, and muscular irritability.
- Distinct from myotonia congenita
- 1980: Alberta probably reported the first sporadic case.
  "Increased mechanical muscle irritability syndrome."

Rippling Muscles
- The direction of rippling is perpendicular to the orientation of the muscle fibers.
- Propagation of contraction is 10x slower than muscle fiber action potential propagation.
  Rippling is (mostly) electrically silent.
- Percussion-Induced Rapid Muscle Contractions
- Percussion-Induced Myoedema
- Muscular Hypertrophy
- Mild CK elevations (<10x upper limit of normal)

### Rippling Muscle Disease

<table>
<thead>
<tr>
<th>Main Symptoms</th>
<th>Hereditary</th>
<th>Acquired/Autoimmune</th>
</tr>
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<tbody>
<tr>
<td>Myalgias; Stiffness ± Weakness</td>
<td>Stiffness; Weakness if MG also present</td>
<td></td>
</tr>
<tr>
<td>CK</td>
<td>Mildly elevated</td>
<td>Mildly elevated</td>
</tr>
<tr>
<td>EMG</td>
<td>Increased Insertional Activity</td>
<td>Increased Insertional Activity</td>
</tr>
<tr>
<td>Treatment</td>
<td>Dantrolene or Calcium Channel blockers (single case reports)</td>
<td>Immunosuppressive medications; Given benign natural history, may not be necessary</td>
</tr>
<tr>
<td>Disease Associations</td>
<td>None</td>
<td>Myasthenia gravis Thymoma</td>
</tr>
<tr>
<td>Other lab findings...</td>
<td>None</td>
<td>Anti-striated muscle antibodies + Ach Receptor antibodies</td>
</tr>
<tr>
<td>Symptom Onset</td>
<td>Childhood</td>
<td>33-60 years old</td>
</tr>
</tbody>
</table>

Show Video of Rippling Muscles

60 year-old man with muscle tightness
Pathophysiology of Rippling

- Mechanical stretch activates the ryanodine receptor → sarcomere contracts → resulting stretch activates adjacent ryanodine receptors → etc.
- Problems with hypothesis:
  - Very large, rapid stretches do not induce direct activation of SR Ca++ release in neonatal rat muscle fibers.
  - Activating 220,000 sarcomeres per second to cause the contraction seems implausible.
  - Why would a stretch affect the T-tubule system anyway?
- Possible Explanation: Combined Mechanical and Electrical Hyperexcitability
Caveolin-3: Normal Gene Product

- Three isoforms (CAV1; CAV2; CAV3)
  - Cav-3 is a muscle-specific protein (cardiac, skeletal, and smooth muscle)
- Roles
  - Sarcolemmal Stability
    - Forms multimers that are the scaffold for caveolae.
    - Caveolae are 50-100 nm invaginations on the sarcolemma.
    - Necessary for normal formation of the T-tubule system.
    - Binds to dystrophin-glycoprotein complex
    - Interacts with dystrophin
  - Signalling
    - Regulates Src kinase and nitric oxide synthase
    - In cardiac muscle, multiple ion channels are targeted to the caveolae
    - Important for myoblast cell differentiation and survival

Caveolin-3: Abnormal Gene Product

- Mutations
  - Dominant-Negative Effect
    - Abnormal gene product sequesters the normal protein in the Golgi apparatus
- Structural Effects
  - Loss of Caveolae
  - T-tubule system derangement
  - Large subsarcolemmal vesicle formation
  - Causes mislocation of dystrophin
- Genotype-phenotype correlations do not exist

Caveolinopathies

- CAV3-Related Distal Myopathy
- CAV3-Related Hypertrophic Cardiomyopathy
- CAV3-Related Isolated HyperCKemia
- CAV3-Related Rippling Muscle Disease
- Limb-Girdle Muscular Dystrophy Type 1C

Final Points

- In patients with hyperCKemia and myalgias (geez...lots of patients), consider caveolinopathy.
- Muscle rippling can have a genetic or autoimmune cause
- If a patient complains of stiffness or myalgias, GO AHEAD AND PERCUSS THE MUSCLE!!
Mutations of CAV3 are NOT associated with:
1. Rippling muscle disease
2. Cardiomyopathy
3. **Retinopathy**
4. Isolated HyperCKemia
5. Limb-Girdle muscular dystrophy

Which of the following is NOT a feature of rippling muscle disease:
1. Percussion-induced rapid muscle contractions
2. Muscle mounding
3. Rippling muscles
4. **Electrical myotonia**

Thanks for Your Attention & Happy Valentine’s Day.