No pain, no gain: a case of exercise-induced rhabdomyolysis

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Case presentation
A 26 year old male presented to neuromuscular clinic for further evaluation of hyperCKemia and possible myopathy.

During childhood, he had 2 episodes of muscle stiffness:

- Generalized stiffness during a hospitalization for a respiratory infection at age 2.
- Brief, mild stiffness of his upper extremities following water rafting at age 10.

He reported having had an extensive neurogenetic workup, including muscle and skin biopsies with no conclusive diagnosis.
Otherwise, he was asymptomatic in childhood and had remained very active throughout his life.

During routine checks, he would have elevated CK and transaminases.

He denied episodes of myalgia or dark urine.
Past medical history: as above

Past surgical history: right shoulder arthroscopy 2012

Medications: none

Allergies: NKA

Family history: Dementia, stroke; no h/o NM disease

Social history: works as a landman- oil and gas; social alcohol consumption, no tobacco or illicit drug use

ROS: fatigue, anxiety

Neurologic exam: unremarkable
Initial diagnostic testing

- Lab studies: Pyruvate, lactic acid, acylcarnitine, free fatty acids, urine organic acids, plasma amino acids, and transaminases (GGT, AST, ALT) all unremarkable

- CK persistently elevated: 3580 at initial visit; 448 when checked 1 month later

- EMG/NCV

- Unable to obtain previous biopsy slides from childhood
### Motor Nerve Conduction:

<table>
<thead>
<tr>
<th>Nerve and Site</th>
<th>Lat ms</th>
<th>Amp mV</th>
<th>Segment</th>
<th>Dist mm</th>
<th>Lat Diff ms</th>
<th>CV m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median.R to Abductor pollicis brevis (C8-T1).R</td>
<td>3.2</td>
<td>13.4</td>
<td>Abductor pollicis brevis (C8-T1)-Wrist</td>
<td>70</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Elbow</td>
<td>7.3</td>
<td>11.8</td>
<td>Wrist-Elbow</td>
<td>245</td>
<td>4.1</td>
<td>60</td>
</tr>
<tr>
<td>Tibial.R to Abductor hallucis (S1-S2).R</td>
<td>4.3</td>
<td>20.0</td>
<td>Abductor hallucis (S1-S2)-Ankle</td>
<td>90</td>
<td>4.3</td>
<td></td>
</tr>
</tbody>
</table>

### Nerve

<table>
<thead>
<tr>
<th>Nerve</th>
<th>M-Lat ms</th>
<th>F-Lat ms</th>
<th>F-Lat Nl ≤ ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibial.R</td>
<td>4.3</td>
<td>46.3</td>
<td>56.0</td>
</tr>
</tbody>
</table>

### Sensory and Mixed Nerve Conduction:

<table>
<thead>
<tr>
<th>Nerve and Site</th>
<th>Onset Lat ms</th>
<th>Peak Lat ms</th>
<th>Amp μV</th>
<th>Segment</th>
<th>Dist mm</th>
<th>CV m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median.R to Digit II (index finger).R</td>
<td>2.4</td>
<td>3.1</td>
<td>44</td>
<td>Wrist-Digit II (index finger)</td>
<td>130</td>
<td>54</td>
</tr>
<tr>
<td>Sural.R to Ankle.R</td>
<td>2.8</td>
<td>3.5</td>
<td>19</td>
<td>Ankle-Lower leg</td>
<td>140</td>
<td>50</td>
</tr>
</tbody>
</table>

### Needle EMG Examination:

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Insertion Activity</th>
<th>Spontaneous Activity</th>
<th>Polytrophy</th>
<th>Amplitude</th>
<th>Duration</th>
<th>Rate</th>
<th>Pattern</th>
<th>Effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibialis anterior (L4-L5).R</td>
<td>Normal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Vastus lateralis (L2-L4).R</td>
<td>Normal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Iliopsoas (L3-L4).R</td>
<td>Normal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Biceps brachii (C5-C6).R</td>
<td>Normal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Few</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
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</table>
Follow-up

- 6 months later, he experienced severe low back pain after an intense cross-fit exercise workout.
  - PCP prescribed pain and steroid medications.
  - That evening he developed dark urine, for which he presented to the ED, and was admitted and treated for rhabdomyolysis.

- CK trend:

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>48,303</td>
<td>55,196</td>
<td>68,762</td>
<td>29,279</td>
<td>6,439</td>
</tr>
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</table>
What would you do next?

- Repeat muscle biopsy?
- Genetic testing?
- Liver US?
- Non-ischemic forearm exercise test?
### Genetic testing

**Myopathy/Rhabdomyolysis**

**Myopathy/Rhabdomyolysis Panel by Massively Parallel Sequencing (BCM-MitomeNGS™)**

#### Overall Results Summary

A heterozygous deletion involving the entire exon 18 of the LPIN1 gene and a heterozygous novel variant of uncertain significance, c.1535+4_1535+7delAGTA, in the LPIN1 gene, were detected.

#### Pathogenic Variant(s)/Mutation(s)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Inheritance</th>
<th>OMIM</th>
<th>Change</th>
<th>Location</th>
<th>Zygosity</th>
<th>Reference(s) / Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPIN1</td>
<td>AR</td>
<td>605518</td>
<td>c.2295-865_2410-30del (p.E766_S838del)</td>
<td>exon 18</td>
<td>heterozygous</td>
<td>PMID: 20583302</td>
</tr>
</tbody>
</table>

#### Variant(s) of Uncertain Significance

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LPIN1 mutation
Recurrent rhabdomyolysis

- Acquired vs. hereditary
  - Metabolic with failure of energy production (mitochondrial FAO defects, inborn errors of glycogenolysis and glycolysis)
  - Structural (muscular dystrophies, myopathies)
  - Problems with calcium pump (RYR1 mutation)
  - Inflammatory (myositis)
- Approximately half of patients will not show a defect in these pathways

Hamel et al., J Inherit Metab Dis (2015)
LPIN1 mutations in mice

>20 years ago: LPIN1 mutations described in mice

- Fatty liver dystrophy, peripheral neuropathy (lipin-1 expression in epineurium, endoneurium, perineurium)
- Insulin resistance, severe hypertriglyceridemia
- Overexpression of lipin-1 in transgenic mice caused obesity

Reue et al., FEBS Letters (2008)
Mammalian lipin family: Lipin-1, Lipin-2, Lipin-3

*LPIN2*: Majeed syndrome- chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia

*LPIN3*: Not known to cause human disease

Csaki et al., *Prog in Lip Res* (2013)
Michot et al., *J Inherit Metab Dis* (2012)
**LPIN1 mutations in humans**

- **Zeharia et al. (2008)**
  - Pediatric patients (n= 3) w/ life-threatening episodes of rhabdomyolysis; mutations in LPIN1 gene (early stop codon)
  - Additional 22 pediatric patients w/ recurrent rhabdomyolysis; identified 5 additional LPIN1 mutations
  - Healthy in between episodes; normal fat distribution, lipid profile, glucose (including during episodes)

- **Michot et al. (2010, 2012)**
  - 29 pediatric patients w/ severe episodes of rhabdomyolysis in infancy
  - 59% cohort lipin-1 deficient (recessive nonsense or frameshift mutations, large-scale deletion)
  - No defects of LPIN2, LIPN3 genes a/w muscular manifestations
Lipin-1 deficiency

- Autosomal recessive
- *LPIN1* mutations 2nd MCC of early-onset recurrent rhabdomyolysis (after FAO defects)
- Rhabdomyolysis episodes usually began before age 6
- MC triggers: febrile illness > prolonged exercise, fasting, anesthesia
- Lipin-1 expressed most in adipocytes and skeletal muscle

Pathogenic mechanism of *LPIN1* mutation causing rhabdomyolysis uncertain

Michot et al., *J Inherit Metab Dis* (2012)
Dual role of lipin-1

Directly interacts w/PPAR-alpha & PGC-1alpha

Reue et al., FEBS Letters (2008)
Triglyceride and phospholipid pathway

Potential treatment strategies
Symptomatic management

- Early detection
- Hyperhydration
- High energy intake from carbohydrates
- Monitoring for complications: hyperkalemia (cardiac monitoring), hypocalcemia, hepatic inflammation; acute renal failure due to myoglobinuria (late)

Establishing anabolism

- Pichler et al. (2015), proposed treatment with high-concentration glucose solution for prevention and early treatment of catabolism to improve prognosis in lipin-1 deficient patients
- Hyperhydration using 3 L/m²/day of 10% glucose (+NaCl, KCl)
- Reduced duration of rhabdomyolysis from 7-10 days (reported in literature) to 5 days (CK <10,000)
Decreasing inflammation

- Catabolic stress (febrile illness, exercise) creates pro-inflammatory state
- High levels of circulating pro-inflammatory mediators chemokines, cytokines (TNF1-alpha, IL-1beta)→ exacerbate lipin-1 deficiency
- Dexamethasone (PGC-1alpha inducer) stimulates lipin-1 expression in adipose and liver, decreases inflammation
- Meijer et al. (2015) used dexamethasone, in addition to standard protocol
  - 4 y/o with LPIN1 mutation and severe clinical course
  - For 2 episodes: dexamethasone 0.6 mg/kg q24 hours (with 1 & 4 repeated doses, respectively)
  - Lower peak CK levels, well-tolerated
Lipin-1 deficiency is an autosomal recessive disorder, common cause for recurrent rhabdomyolysis with onset in childhood.

Lipin-1 most commonly expressed in skeletal muscle, adipocytes; role in TAG and phospholipid metabolism, mitochondrial energy pathway.

Potential treatment strategies to reduce severity and duration of rhabdomyolysis episodes include:

- High concentration glucose solution (anabolism)
- Dexamethasone (stimulates lipin-1 expression, anti-inflammatory)


