A Tremulous and Floppy Infant with Cardiomyopathy

**Michael A. Lopez, MD, PhD, Pediatric Neuromuscular Fellow**
Caro Tesi-Rocha, MD, Sarada Sakamuri, MD, Seth Lummus, DO, Hannes Vogel, MD, John W. Day, MD, PhD

Division of Neuromuscular Medicine & Division of Neuropathology
Stanford University
Chief Complaint

- A former 39-week large for gestational age male infant with known cardiomyopathy presented at 3 months of age
  - Respiratory distress
  - Hypoglycemia
  - Cardiogenic shock requiring extracorporeal membranous oxygen exchange
- How did we get here?
Birth Hospital Course

- At birth
  - Poor feeding + respiratory distress
  - Tremors and ankle clonus
    - Reflexes brisk
      - 3+ at knees with spread
      - 4+ at ankles with sustained 10 beat clonus
  - Hypotonia
    - Slip through
    - Marked head lag
Birth Hospital Course

- Labs normal (CK 111 U/L, ammonia 53 umol/L, lactate 1.2)
- Echocardiogram: hypertrophic obstructive cardiomyopathy
  - Enlarged right ventricle and septum
  - Normal systolic function (LVEF 75% → 58%)
  - Evidence of diastolic dysfunction
- Normal newborn screen, chromosomal microarray, MRI brain, and cEEG
- Cardiomyopathy and glycogen storage panels ordered
Birth Hospital Course

- Feeding improved
- Respiratory distress improved
- Interval echocardiogram “without changes”
- Discharged home after 3 weeks with close follow up
Differential considerations that include tremor, hypotonia, and cardiomyopathy?

Localization?
Presentation at 3 months-old with cardiogenic shock

- Initially, he did well at home
  - Tracking
  - Smiling
  - Cooing
- 2 weeks prior to presentation (several PCP visits)
  - Progressive feeding difficulties
  - Respiratory distress
  - Lethargy
- Brought to hospital
  - Cardiogenic shock
  - Required ECMO
  - Parainfluenza +
Additional History & Exam

- Genetic results, 2 variants
  - Pathogenic variant
  - Variant of uncertain significance
- Neuromuscular team consulted
  - Normal facial expression without myopathic facies
  - No dysmorphic features in his face
  - Normal muscle bulk
  - Appendicular hypotonia
- Recommendations
  - Muscle biopsy
Vastus Lateralis Biopsy – H&E

Numerous small round fibers
Vastus Lateralis Biopsy – ATPase pH 9.4

Selective type 1 fiber hypertrophy
Vastus Lateralis Biopsy – ATPase pH 4.3

Selective type 1 fiber hypotrophy
Do we have a molecular diagnosis?

Is myopathy progressive?

What role does myopathy play in any considerations for transplant?
Diagnosis

- Compound heterozygous variants in found in **MYL2 gene** with
  - Paternal pathogenic variant: **c.184A>T, p.Lys62***
  - Maternal variant of unknown significance: **c.122A>T, p.Asp41Val**
- **MYL2** encodes myosin regulatory light chain

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**Table 2** Global scheme of main myosins and major muscle fibre types in adult human skeletal muscle and heart

<table>
<thead>
<tr>
<th>Myosin</th>
<th>Adult heart</th>
<th>Myosin gene</th>
<th>Adult skeletal muscle</th>
<th>Myosin gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myosin heavy chain</td>
<td></td>
<td><strong>MYH6</strong></td>
<td>Type 2A: myosin IIa, fast</td>
<td><strong>MYH2</strong></td>
</tr>
<tr>
<td></td>
<td>Type-α, atrial isoform</td>
<td></td>
<td>Type 2B: myosin IIx/d, fast</td>
<td><strong>MYH1</strong></td>
</tr>
<tr>
<td></td>
<td>Type-β, ventricular isoform</td>
<td><strong>MYH7</strong></td>
<td>Type 1, slow</td>
<td><strong>MYH7</strong></td>
</tr>
<tr>
<td>Myosin essential/alkali light chain</td>
<td>Atrial isoform</td>
<td><strong>MYL1</strong> (MYL4)</td>
<td>Fast</td>
<td><strong>MYL1</strong></td>
</tr>
<tr>
<td></td>
<td>Ventricular isoform</td>
<td><strong>MYL3</strong></td>
<td>Slow</td>
<td><strong>MYL3</strong> (MYL6B)</td>
</tr>
<tr>
<td>Myosin regulatory light chain</td>
<td>Atrial isoform</td>
<td><strong>MYL7</strong></td>
<td>Fast</td>
<td><strong>MYLPF</strong></td>
</tr>
<tr>
<td></td>
<td>Ventricular</td>
<td><strong>MYL2</strong></td>
<td>Slow</td>
<td><strong>MYL2</strong></td>
</tr>
</tbody>
</table>

**MYL2-associated myosinopathy**

- Dominant mutations linked with cardiomyopathy
- Recessive mutations linked with heart + skeletal myopathies:
  - Italian families with compound heterozygous mutations
  - Dutch families with homozygous mutations
- All patients
  - Died by 4 to 6 months
  - Clonus / tremor
    - Generalized high amplitude tremor + clonus
    - Present at birth prior to cardiomyopathy symptoms
- Hallmarks were
  - Rapidly progressive myopathy
  - Myofibrillar disarray
  - Cardiomyopathy

Concluding Thoughts

- **Myosinopathies** should be considered in patients with tremor, hypotonia, and cardiomyopathy.
- Genetic testing in this patient revealed pathogenic variants in *MYL2* gene associated with **congenital myopathy** and **cardiomyopathy**.
- *MYL2* mutations can be **rapidly fatal** in first 3 to 4 months of life due to cardiomyopathy.
- **Heart transplantation** went well for this patient and he continues to make developmental progress without striking weakness.
- Prognosis unclear, but seems to have **milder congenital myopathy**.
Thank You!

References:

Additional thanks to:
- Neuromuscular Faculty
- Adult and Pediatric MDA teams