A Tremulous and Floppy Infant with Cardiomyopathy

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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

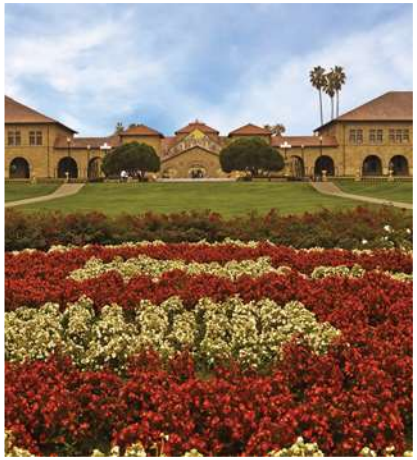
- Labs normal (CK 111 U/L, ammonia 53 umol/L, lactate 1.2)
- Echocardiogram: hypertrophic obstructive cardiomyopathy
  - Enlarged right ventricle and septum
  - Normal systolic function (LVEF 75% → 58%)
  - Evidence of diastolic dysfunction
- Normal newborn screen, chromosomal microarray, MRI brain,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



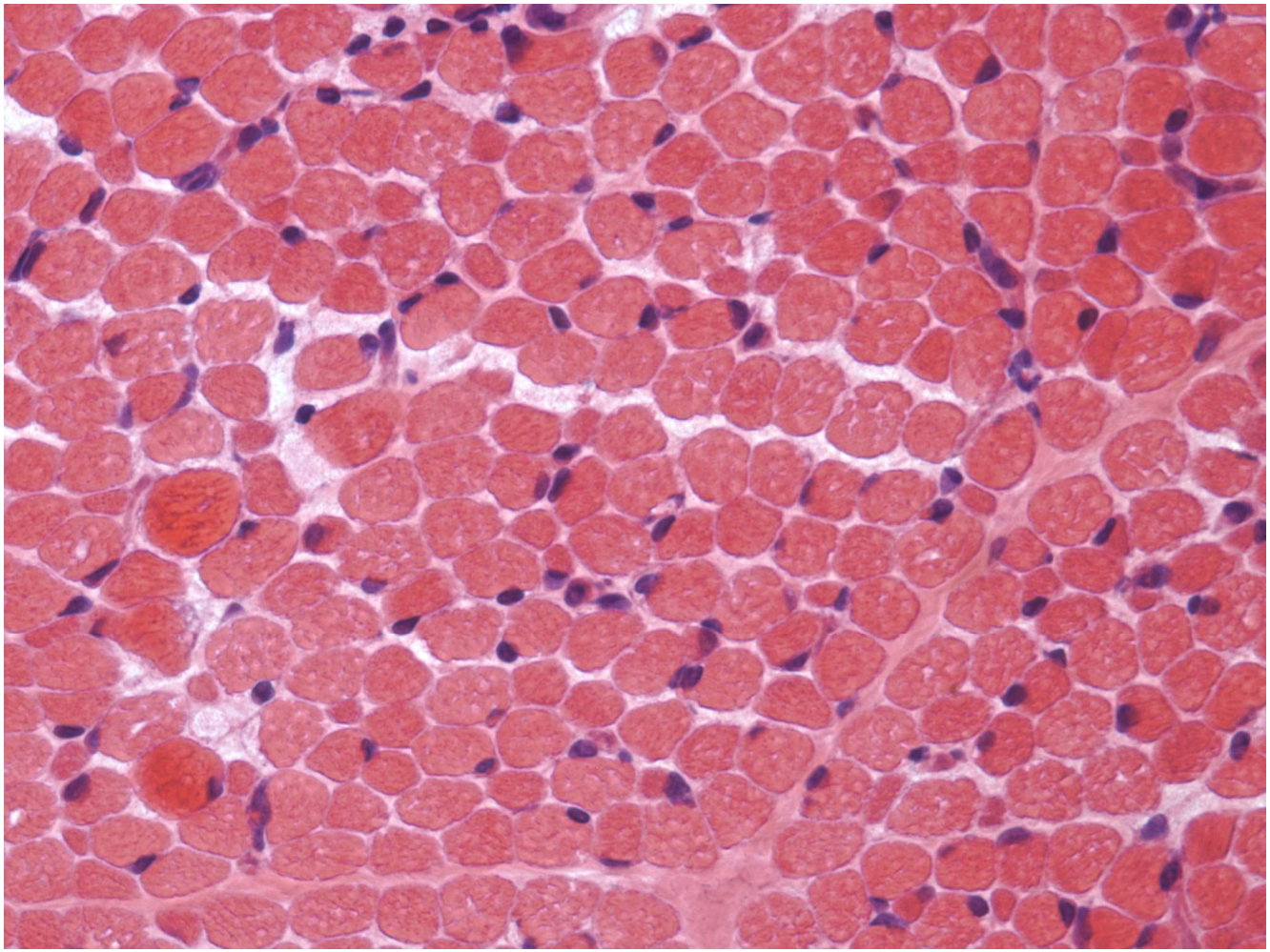
Presentation at 3 months-old with cardiogenic shock

- 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

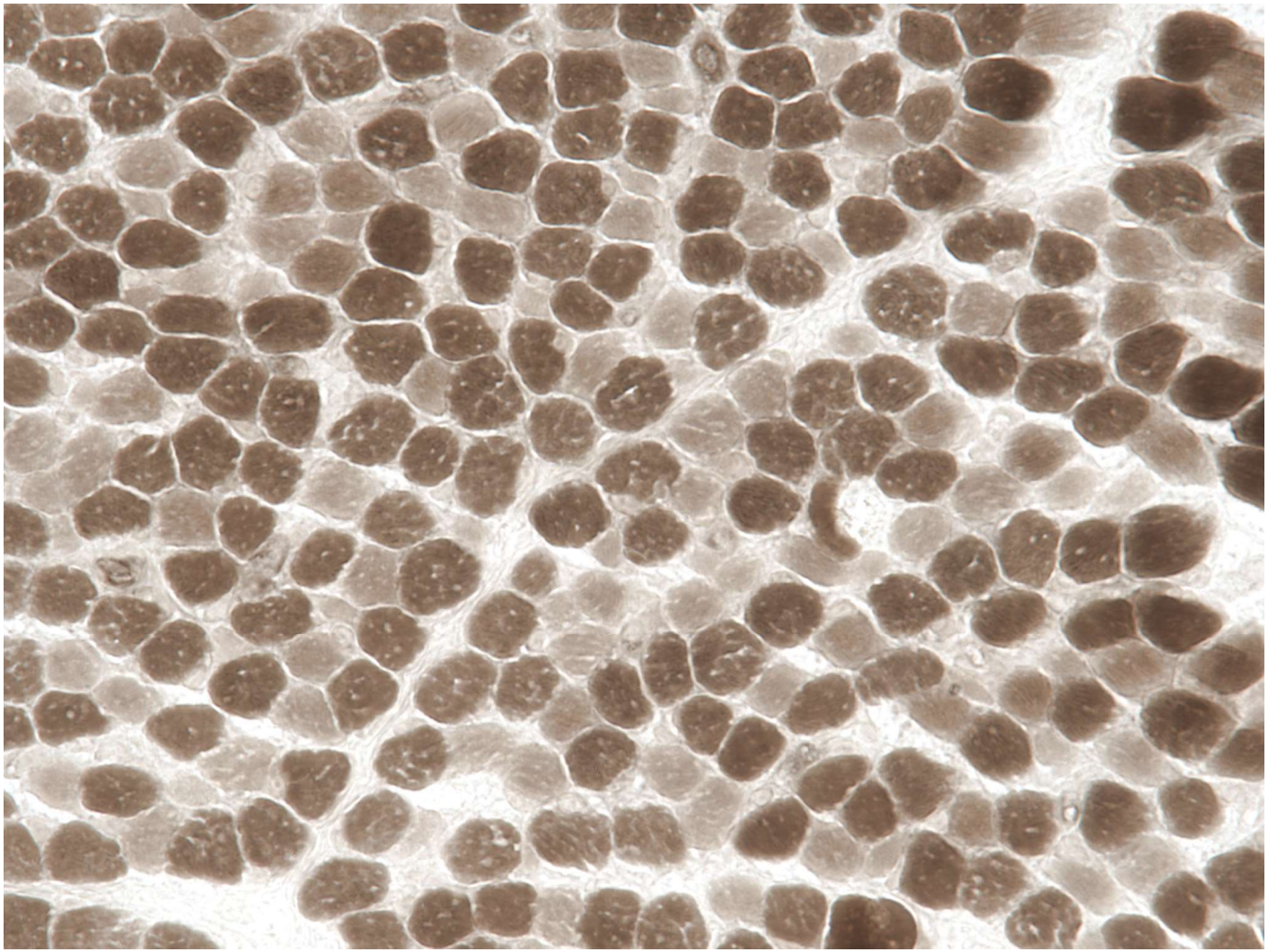
- Genetic results, 2 variants
  - Pathogenic variant
  - Variant of uncertain significance
- Neuromuscular team consulted
  - Normal facial expression without myopathic facies
  - No dysmorphic features in his face
  - Normal muscle bulk
  - Appendicular hypotonia
- Recommendations
  - Muscle biopsy

Vastus Lateralis Biopsy – H&E



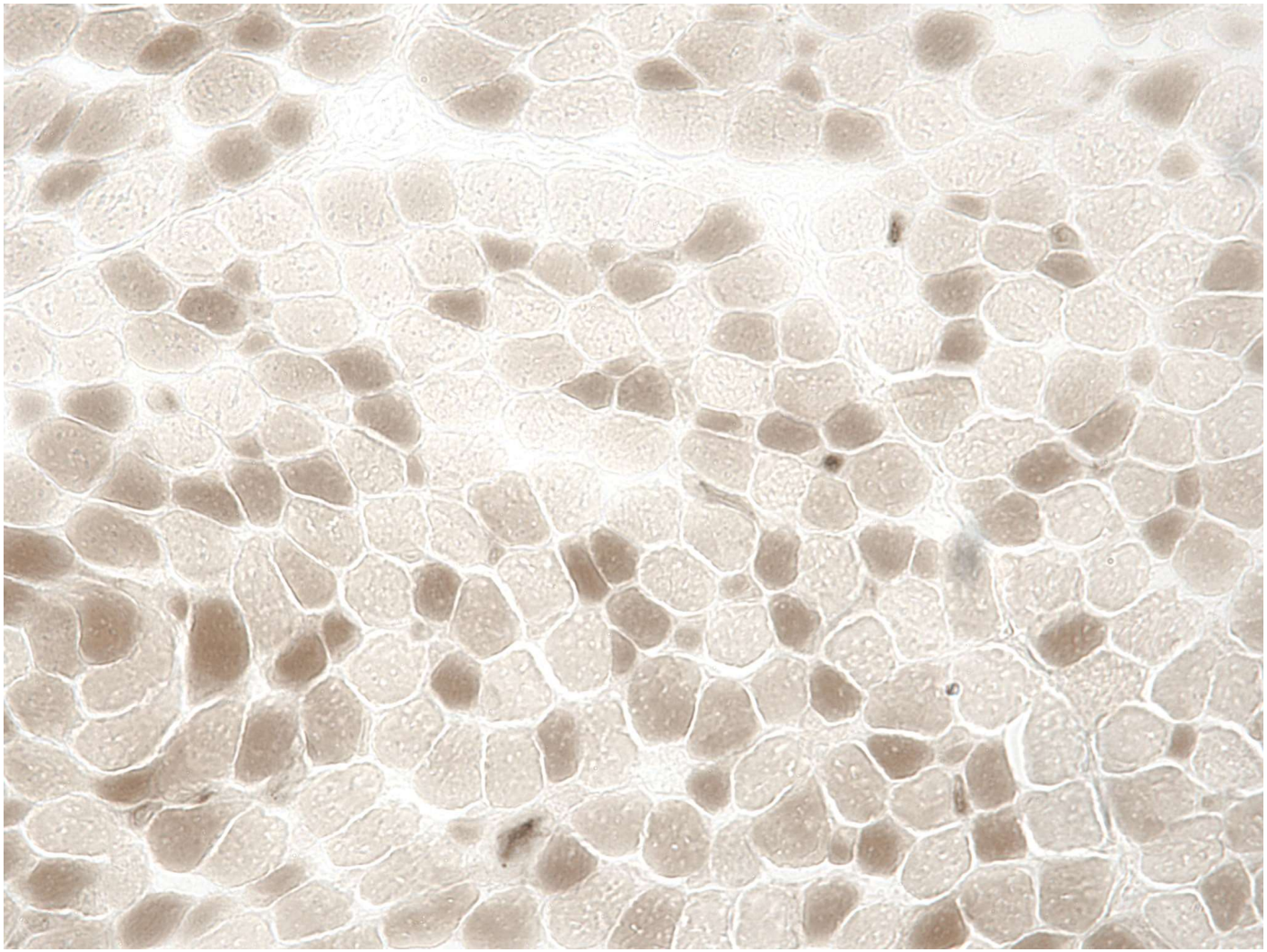
Numerous small round fibers

Vastus Lateralis Biopsy – ATPase pH 9.4



Selective type 1 fiber hypotrophy

Vastus Lateralis Biopsy – ATPase pH 4.3

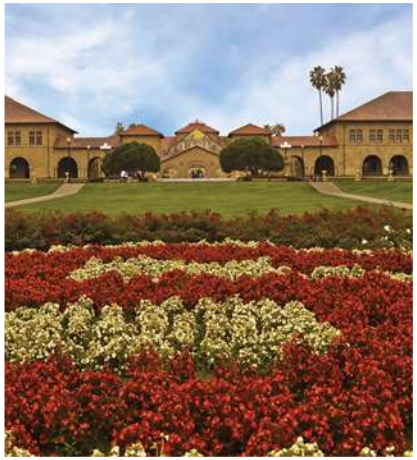


Selective type 1 fiber hypotrophy

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

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

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

Wterman, MAJ, et. Al. Brain 2013: 136; 282-293

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

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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:

1. Recessive MYL2 mutations cause infantile type I muscle fibre disease and cardiomyopathy. Marian A. J., Frank Baas, et. Al.. Brain 2013: 136; 282-293

Additional thanks to:

- Neuromuscular Faculty
- Adult and Pediatric MDA teams