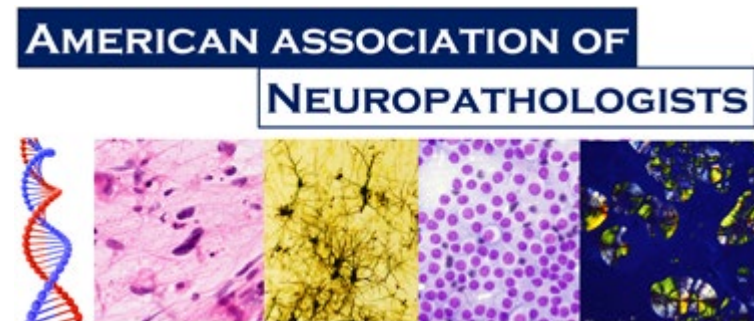


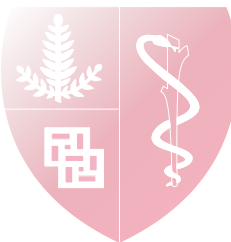
CASE 2020-8

Saman Ahmadian M.D. and Hannes Vogel M.D.
Neuropathology
Stanford University



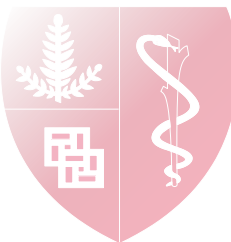
Disclosure

- We have no financial relationships to disclose

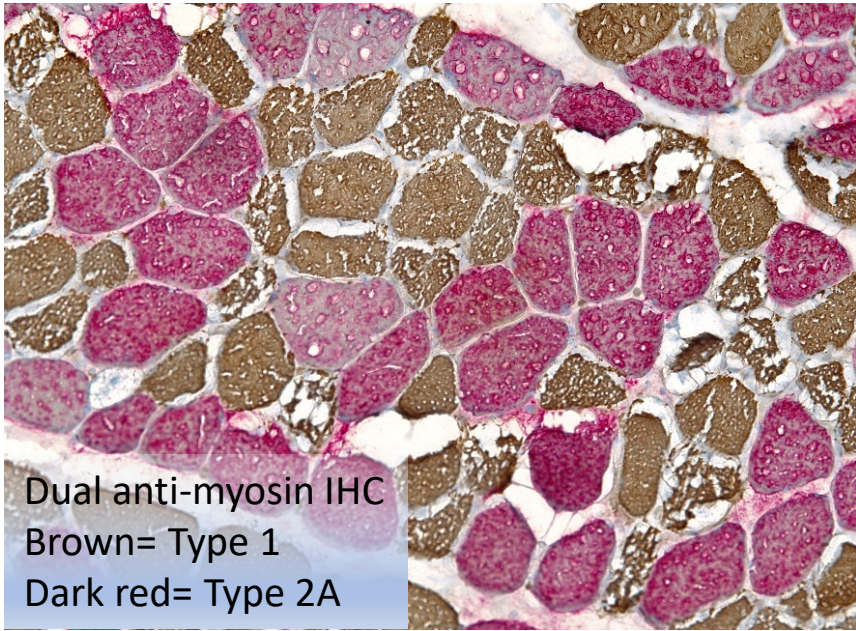
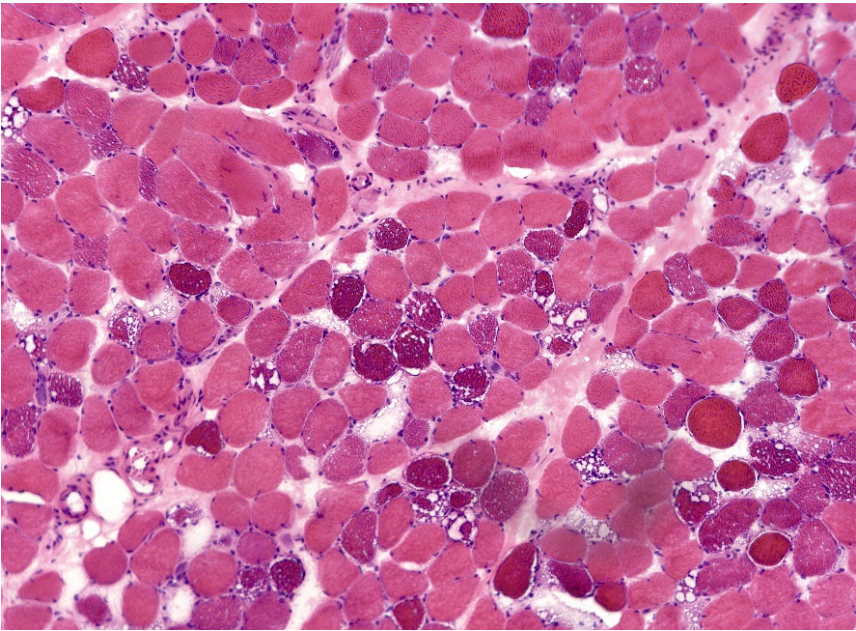


Clinical history

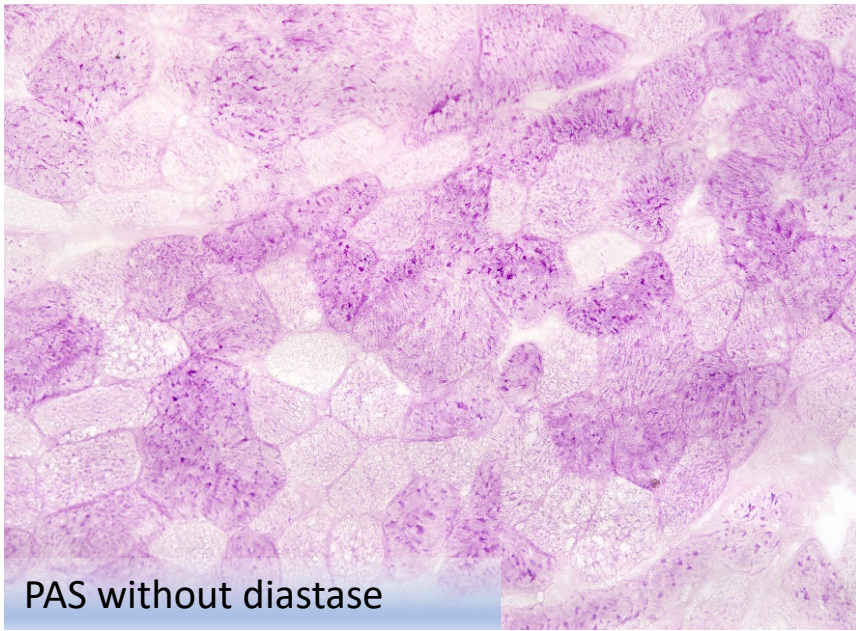
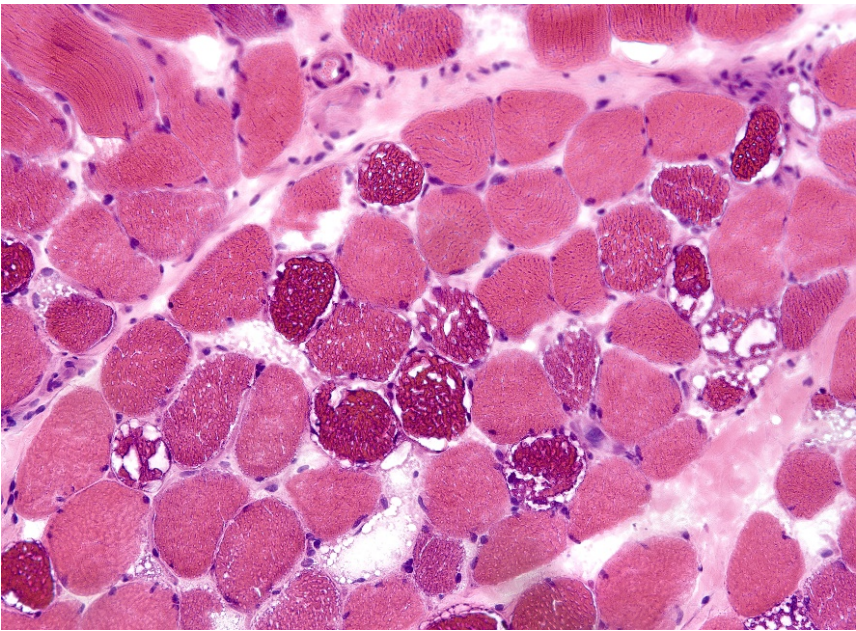
- A 38-year-old female with onset of persistent post-exercise soreness in her legs, 10 months before biopsy; a history of being athletic and hiking without issues
- Elevated CK; varied between 288 and 1089
- Brief improvement on steroids and hydroxychloroquine then subsequently showed a further decline
- Gradual progression of leg weakness, with progression to her arms, fatigue with chewing and jaw pain
- EMG: unremarkable
- Negative/normal myositis panel, AST/ALT of 106/91, positive ANA and anti ds-DNA
- Muscle biopsy performed followed by high dose prednisone, mycophenolate mofetil, and IVIG, with mild improvement of symptoms



Deltoid and quadriceps muscle biopsies

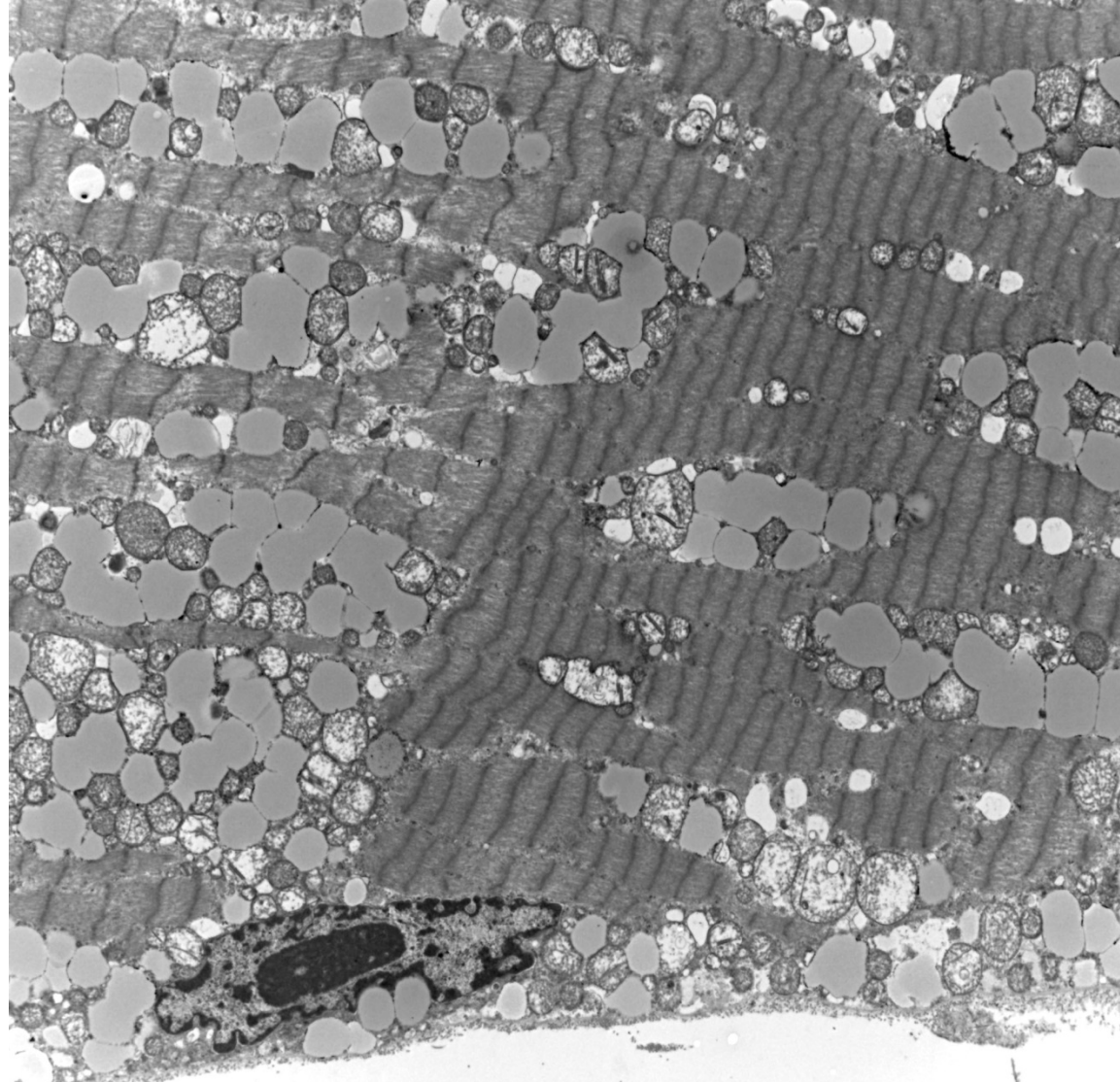


Dual anti-myosin IHC
Brown= Type 1
Dark red= Type 2A

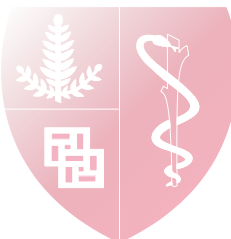
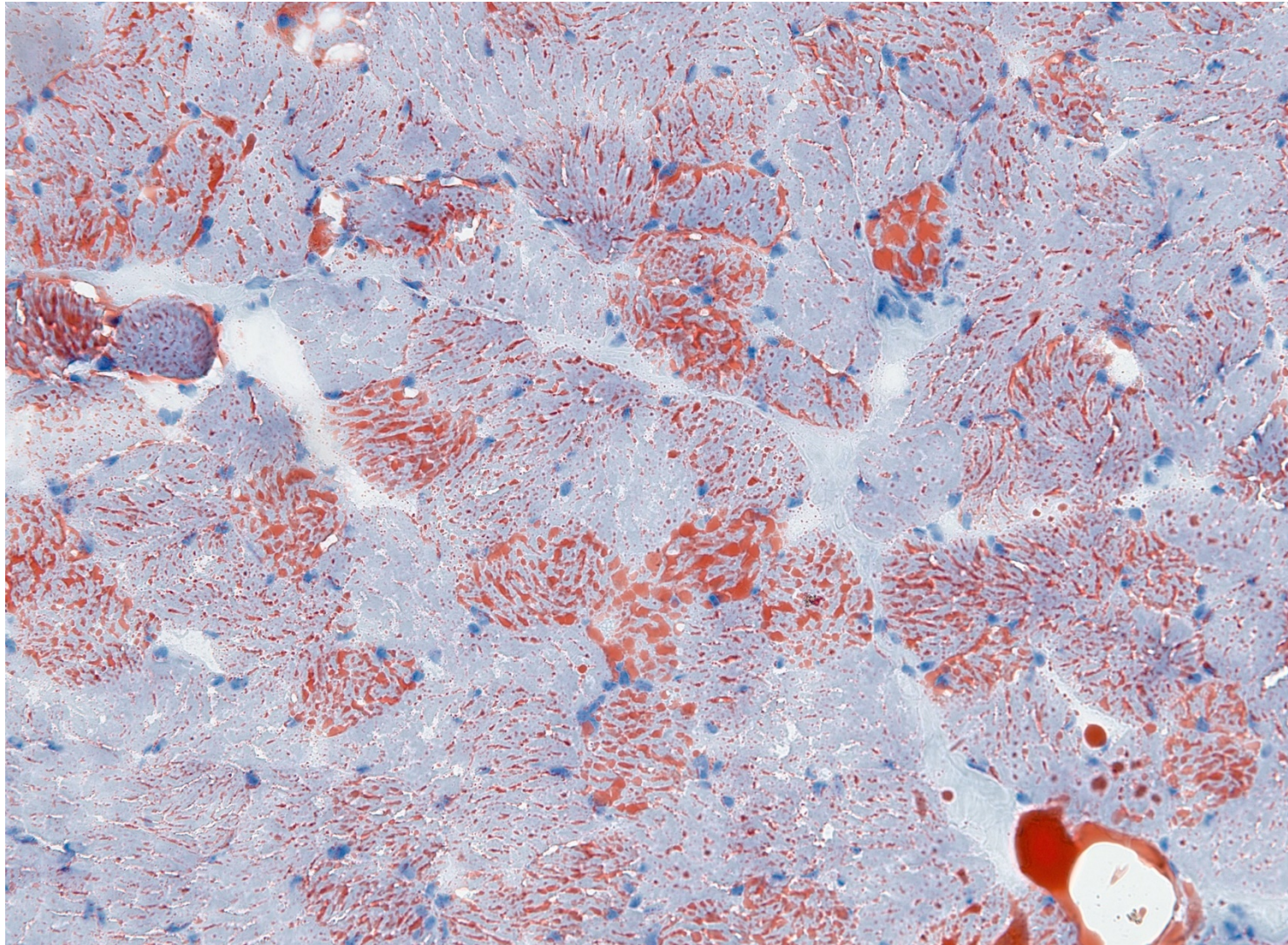


PAS without diastase

Electron microscopy

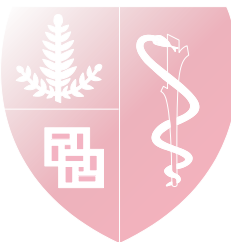


Oil-Red-O

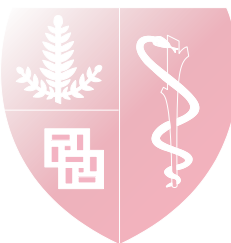


Muscle biopsy biochemical results

- Reduced carnitine levels
- Reduced PFK activity
- Normal acid and neutral maltase activity
- Elevated CPT2 activity



Neuropathological diagnosis



Preliminary diagnosis: Lipid storage myopathy

Differential diagnosis of lipid storage myopathies

Preliminary diagnosis: Metabolic myopathy suggestive of lipid myopathy

- Malnutrition; HIV

Enzyme and genetic testing

- Carnitine deficiency (OCTN2 gene)

- Reduced skeletal muscle carnitine levels

- Fatty acid oxidation disorders (neutral maltase and CPT2 activities)

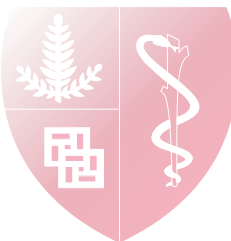
- CPT2 deficiency (*CPT2*) and nuclear genome panel: two heterozygous pathogenic variants in the

- *Carnitine transferase 2* gene
- Acyl-CoA dehydrogenase deficiencies (SCAD, MCAD, LCAD, VLCAD, MADD)

- Neutral lipid storage diseases

- Neutral lipid storage disease with myopathy (*PNPLA2*)
- Neutral lipid storage disease with ichthyosis (*CGI58*)

- Mitochondrial myopathies



Lipid storage myopathies

	Subtypes	Symptoms	Muscle histology	Genetic
Carnitine deficiency	-Myopathic form - -Systemic form	-Childhood, -Symmetric proximal weakness - +/- cardiomyopathy and facial weakness	-Severe lipid storage -Mitochondrial proliferation and ultrastructural abnormalities	<i>OCTN2</i> (AR) Carnitine
CPT2 deficiency	-Neonatal -Infantile -Adult	-Recurrent muscle pains -Myoglobinuria (precipitated by prolonged fasting or exercise)	-Normal -Regenerative fibers/necrosis only present in biopsies taken soon after the onset of symptoms, -Increased lipid (50%)	<i>CPT2</i> (Recessive & Semi-Dominant)
Neutral lipid storage disease	-Childhood or adult -With myopathy -With ichthyosis	-Intellectual disability (66%) -Cardiomyopathy (33%) -Proximal & distal asymmetric weakness: difficulty walking	-Massive lipid accumulation and lipid vacuoles, Types 1 & 2 fibers	<i>PNPLA2</i> (AR) <i>CGI58</i>



Lipid storage myopathies

	Subtypes	Symptoms	Muscle histology	Genetic
Acyl-CoA dehydrogenase deficiencies	Short chain (infantile/adult)	-FTT, hypotonia/dystonia, seizures (22%); dysmorphic facies -Muscle weakness	Mild variation in fiber size and variable lipid storage in Types 1 and 2 fibers	Depends on the subtype
	Medium chain (infantile/adult)	-Hypoketotic hypoglycemia -Muscle fatigue, pain, reduced exercise tolerance		
	Long chain (early childhood)	- Hypoketotic hypoglycemia, cardiac arrest - Hepatomegaly, cardiomegaly, hypotonia		
	Very long chain (infantile/adult)	-Myalgic episodes, with severe pain -Rhabdomyolysis		
	Multiple acyl-CoA dehydrogenase (MADD) (infantile/adult)	-Proximal weakness -Hepatomegaly -Episodes of metabolic crises -Urine: High glutaric & ethylmalonic acids	Lipid accumulation, Type 1 fibers	<i>ETFA, ETFB, ETFDH</i> (AR)

Preliminary diagnosis: Lipid storage myopathy

Differential diagnosis of lipid storage myopathies

Preliminary diagnosis: Metabolic myopathy suggestive of lipid myopathy

~~• Malnutrition; HIV~~

Enzyme and genetic testing

• Carnitine deficiency (OCTN2 gene)

◦ Reduced skeletal muscle carnitine levels

• Fatty acid oxidation disorders (acyl-CoA oxidase, acyl-CoA dehydrogenase, acyl-CoA oxidase 2, long chain acyl-CoA oxidase, acyl-CoA oxidase 3, acyl-CoA oxidase 4, acyl-CoA oxidase 5, acyl-CoA oxidase 6, acyl-CoA oxidase 7, acyl-CoA oxidase 8, acyl-CoA oxidase 9, acyl-CoA oxidase 10, acyl-CoA oxidase 11, acyl-CoA oxidase 12, acyl-CoA oxidase 13, acyl-CoA oxidase 14, acyl-CoA oxidase 15, acyl-CoA oxidase 16, acyl-CoA oxidase 17, acyl-CoA oxidase 18, acyl-CoA oxidase 19, acyl-CoA oxidase 20, acyl-CoA oxidase 21, acyl-CoA oxidase 22, acyl-CoA oxidase 23, acyl-CoA oxidase 24, acyl-CoA oxidase 25, acyl-CoA oxidase 26, acyl-CoA oxidase 27, acyl-CoA oxidase 28, acyl-CoA oxidase 29, acyl-CoA oxidase 30, acyl-CoA oxidase 31, acyl-CoA oxidase 32, acyl-CoA oxidase 33, acyl-CoA oxidase 34, acyl-CoA oxidase 35, acyl-CoA oxidase 36, acyl-CoA oxidase 37, acyl-CoA oxidase 38, acyl-CoA oxidase 39, acyl-CoA oxidase 40, acyl-CoA oxidase 41, acyl-CoA oxidase 42, acyl-CoA oxidase 43, acyl-CoA oxidase 44, acyl-CoA oxidase 45, acyl-CoA oxidase 46, acyl-CoA oxidase 47, acyl-CoA oxidase 48, acyl-CoA oxidase 49, acyl-CoA oxidase 50, acyl-CoA oxidase 51, acyl-CoA oxidase 52, acyl-CoA oxidase 53, acyl-CoA oxidase 54, acyl-CoA oxidase 55, acyl-CoA oxidase 56, acyl-CoA oxidase 57, acyl-CoA oxidase 58, acyl-CoA oxidase 59, acyl-CoA oxidase 60, acyl-CoA oxidase 61, acyl-CoA oxidase 62, acyl-CoA oxidase 63, acyl-CoA oxidase 64, acyl-CoA oxidase 65, acyl-CoA oxidase 66, acyl-CoA oxidase 67, acyl-CoA oxidase 68, acyl-CoA oxidase 69, acyl-CoA oxidase 70, acyl-CoA oxidase 71, acyl-CoA oxidase 72, acyl-CoA oxidase 73, acyl-CoA oxidase 74, acyl-CoA oxidase 75, acyl-CoA oxidase 76, acyl-CoA oxidase 77, acyl-CoA oxidase 78, acyl-CoA oxidase 79, acyl-CoA oxidase 80, acyl-CoA oxidase 81, acyl-CoA oxidase 82, acyl-CoA oxidase 83, acyl-CoA oxidase 84, acyl-CoA oxidase 85, acyl-CoA oxidase 86, acyl-CoA oxidase 87, acyl-CoA oxidase 88, acyl-CoA oxidase 89, acyl-CoA oxidase 90, acyl-CoA oxidase 91, acyl-CoA oxidase 92, acyl-CoA oxidase 93, acyl-CoA oxidase 94, acyl-CoA oxidase 95, acyl-CoA oxidase 96, acyl-CoA oxidase 97, acyl-CoA oxidase 98, acyl-CoA oxidase 99, acyl-CoA oxidase 100)

~~• CPT2 deficiency (CPT2)~~

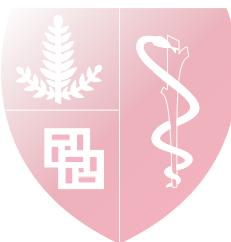
• Acyl-CoA dehydrogenase deficiencies (SCAD, MCAD, LCAD, VLCAD, MADD)

~~• Neutral lipid storage diseases~~

~~• Neutral lipid storage disease with myopathy (PNPLA2)~~

~~• Neutral lipid storage disease with ichthyosis (CGI58)~~

• Mitochondrial myopathies



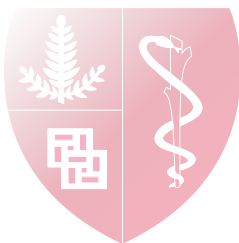
Genetic testing:

- Dual mitochondrial and nuclear genome panel: two heterozygous pathogenic variants in the nuclear *ETFDH* gene, but with unknown phase

Enzyme and genetic testing

Gene	Inheritance	OMIM	Change	Location	Zygoty
ETFDH	AR	231675	c.265C>T (p. R86C)	Exon 3	Heterozygous
ETFDH	AR	231675	c. 488-1G>T (splice site)	Intron 4	Heterozygous

nuclear ETFDH gene



Final diagnosis

Lipid storage myopathy consistent with Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) OMIM 231680, late onset form, AKA glutaric acidemia IIC

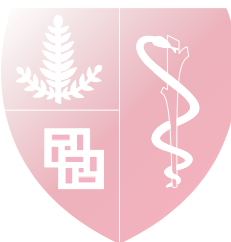
- Reduced skeletal muscle carnitine levels
- Normal acid and neutral maltase and CPT2 activities
- Dual mitochondrial and nuclear genome panel: two heterozygous pathogenic variants in the nuclear ETFDH gene



Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)

AKA: Glutaric acidemia/aciduria II

- AR disorder associated with deficiency of either an electron-transfer flavoprotein (ETF, encoded by *ETF A* and *ETF B*) or dehydrogenase (ETF₂FDH, encoded by *ETF₂FDH*)
- Allelic with Coenzyme Q10 deficiency
- Clinical presentations
 - **Neonatal-onset form with congenital anomalies** (type I): renal cystic dysplasia and other congenital anomalies; death in the first few weeks
 - **Neonatal-onset form without congenital anomalies** (type II): infants and children, episodic hypoglycemia, acidosis, and hepatomegaly
 - **Late-onset form** (type III)



Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)

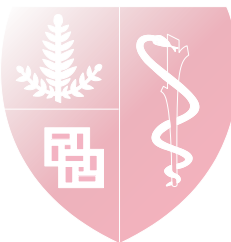
AKA: Glutaric acidemia/aciduria II

- **Late-onset form (type III):**
 - Symptoms and age at presentation are highly variable, with recurrent episodes of lethargy, hypoglycemia, metabolic acidosis, and hepatomegaly
 - Muscle involvement in the form of pain, weakness, and lipid myopathy
 - EMG: myopathic or neuropathic
 - Lab: High CK; muscle chemistry: low carnitine
 - Almost all patients with late-onset MADD (98%) are responsive to riboflavin



Follow up

- The mother's genetic testing showed that the mutation was trans in the patient and thus, disease-causing
 - Preliminary diagnosis: Metabolic myopathy suggestive of lipid myopathy
- Since stopping the hydroxychloroquine, the patient reported improvement, she is able to walk and return to work with some residual proximal weakness in the lower extremities
 - Enzyme and genetic testing
- A prescription of riboflavin 100mg given and a recommendation to consider carnitine, CoQ10, and to maintain a low fat, high carbohydrate diet
 - Reduced skeletal muscle carnitine levels
 - Normal acid and neutral maltase and CPT2 activities
 - Deaf mitochondrial and nuclear genomic panel: two heterozygous pathogenic variants in the nuclear ETFDH gene
- Verbal follow-up from the patient was that she “feels a difference with the vitamin B and dietary change”



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