A 38-year-old woman with reversible proximal limb weakness and dyspnea

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Clinical presentation:

A 38-year-old woman presented with nine months of proximal leg and arm weakness and dyspnea. She initially noted leg weakness after a six-mile hike. She denied distal limb weakness, myalgias, dysphagia, dysarthria, ptosis, diplopia, arthralgias, or rash. She is otherwise healthy, met all her developmental milestones, and has no family history of neuromuscular disease. She was on no medications.

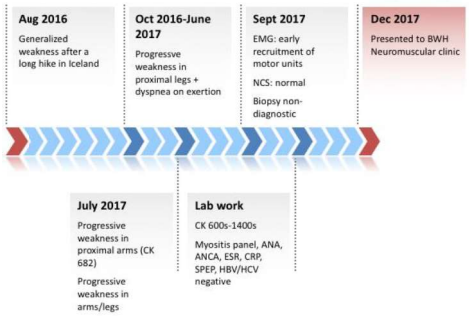
Laboratory values were remarkable for:
- Creatine kinase 600-1400s U/L
- Aldolase 8.7 U/L
- Alanine aminotransferase 77 U/L
- Aspartate aminotransferase 95 U/L
- Negative: myositis panel, ANA, ANCA, ESR, CRP, SPEP, HBV/HCV

Pulmonary function tests were normal.

Electromyogram:
- Fibrillations and positive sharp waves in the right thoracic paraspinals and right medial gastrocnemius
- Polyphasic motor units in the right iliopsoas, deltoid, vastus lateralis, biceps femoris, and infraspinatus muscles.

She had a right gastrocnemius biopsy at an outside medical center that was unremarkable.

She was referred to Brigham and Women's Hospital for further evaluation.



Additional workup

Cranial nerves: II-XII intact

Motor:
- Normal bulk and tone without fasciculations.
- She had bilateral scapular winging.
- Her strength was (Medical Research Council grade (MRC); right/left when applicable):
  - neck flexion 4-; neck extension 5
  - shoulder abduction 4
  - elbow flexion 4/4; elbow extension 4+/4+
  - wrist and finger flexion and extension 5/5
  - hip flexion 4/4; hip extension and abduction 3-/3-
  - knee flexion 4/4; knee extension 4+/4+
  - ankle dorsi- and plantarflexion 5/5

Sensation: intact to all modalities.

Reflexes: 2+ at the biceps and 1+ elsewhere (downgoing toes).

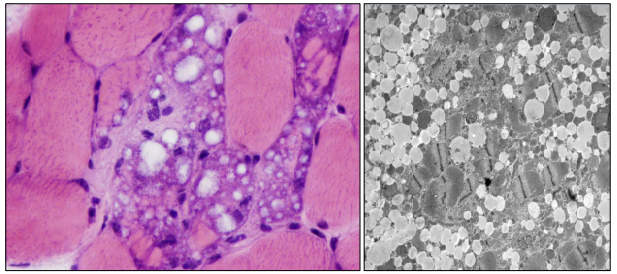
Gait: she had a waddling gait and used her upper body to stand from a seated position.

Labs: Pompe and LGMD negative, several acylcarnitine species elevated, free carnitine slightly low, total carnitine normal, urine organic acid with elevation in 2-hydroxy glutaric acid

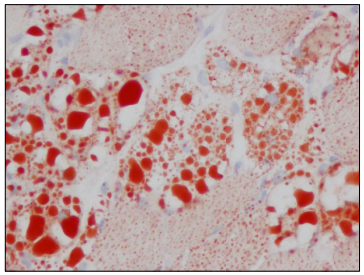
Repeat EMG/NCS: myopathic process

Biopsy

Right Deltoid

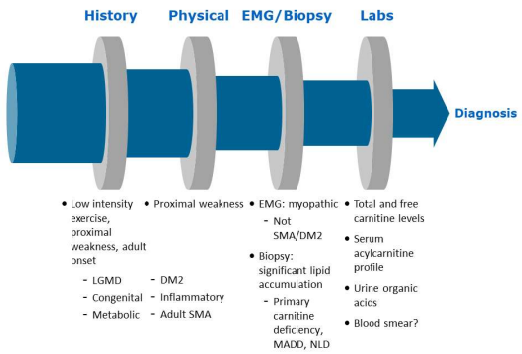


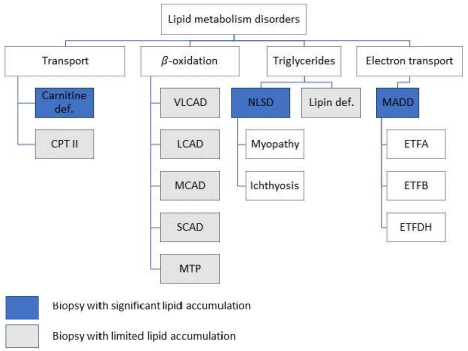
H&E, 400x — Electron Microscopy



Oil Red O, 200x

Clinical Approach





CPT II: carnitine palmitoyltransferase II; VLCAD: very long-chain acyl-CoA dehydrogenase; LCAD: long-chain acyl-CoA dehydrogenase; MCAD: medium-chain acyl-CoA dehydrogenase; SCAD: short-chain acyl-CoA dehydrogenase; MTP: mitochondrial trifunctional protein; NLSD: neutral lipid storage disease; MADD: multiple acyl-CoA dehydrogenase deficiency; ETFA/B: electron-transfer flavoprotein subunits alpha and beta; ETFDH: electron-transfer flavoprotein dehydrogenase

Outcome

Riboflavin 400 mg + CoQ10 100 mg daily were started with significant clinical improvement in her fatigue and strength (MRC R/L, when applicable):
- neck flexion 4+
- shoulder abduction 5/5
- elbow flexion/extension 5/5
- hip flexion/extension/abduction 4/4
- knee flexion 5-/5-, knee extension 5/5

Genetic analysis showed ETFDH mutations:
- c.814 G>A, p.Gly272Arg, heterozygous, likely pathogenic and known (reported in 2 cases)
- c.1204 A>G, p.Thr402Ala, heterozygous, variant of uncertain significance, and novel.

Discussion

The patient presented with adult-onset, subacute proximal weakness with ETFDH mutations causing riboflavin-responsive MADD.

MADD phenotype (highly heterogeneous):
- *Neonatal*: congenital anomalies, multisystem involvement (metabolic decompensations, cardiomyopathy), death in the newborn period
- *Neonatal/childhood*: myopathy, encephalopathy, cardiomyopathy, episodic vomiting/diarrhea
- *Adult*: myopathy and premature fatigue with typically less severe metabolic derangements, hepatomegaly, episodic vomiting/diarrhea, and cardiomyopathy

Workup and Diagnosis:
- *Exam*: proximal, axial weakness
- *Muscle biopsy*: lipid-filled vacuoles
- *EMG/NCS*: myopathic-appearing MUAPs, may have axonal sensory neuropathy
- *Labs* (may only be abnormal during metabolic decompensations):
  - *Free carnitine*: slightly low to normal
  - *Acylcarnitine profile (serum)*: elevated short-, medium-, and long-chain acylcarnitines
  - *Urine organic acids*: normal to elevations in medium-chain dicarboxylic acids, glutaric aciduria
- *Genetics*: ETFA (5%), ETFB (2%), ETFDH (93%)
- *Misdiagnosed* as polymyositis

Treatment:
- Late-onset MADD: riboflavin-responsive in 98% of cases
- Riboflavin 100-400 mg daily + CoQ10 50-100 mg daily + Carnitine 2-4 g daily
- Avoid fasting and enjoy a low-fat diet

References

- Grünert, Sarah C. *Orphanet Journal of Rare Diseases*, BioMed Central, 2014.
- Zhu, Min, et al. *Journal of Human Genetics*, 2014.
- Laforet, Pascal, and Christine Vianey-Saban. *Neuromuscular Disorders*, 2010.