1.2 Million CK Caused by Rare Fatty Acid Oxidation Disorder

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Introduction

- Rhabdomyolysis is a condition of muscle necrosis causing muscle pain and release of creatinine kinase (CK) into the circulation.
- There are extremely rare hereditary myopathies that result in recurrent rhabdomyolysis and can lead to renal failure.
- These disorders stem from disruption in mitochondrial beta-oxidation or transportation of fatty acids via the carnitine pathway resulting in hypoketotic hypoglycemia, deposition of fat causing liver steatosis, cardiomyopathy, altered mentation, and myopathy.
- Fatty acid oxidation disorders of interest include short chain acyl-coA dehydrogenase deficiency, carnitine palmitoyltransferase type 1 (CPT1D) and type 2 deficiency (CPT2D). (1-3, 7) (Figure 2)
- Initial diagnosis is made based on symptoms, acylcarnitine elevations, urine organic acid quantification, and is confirmed via genetic testing. (5)
- CPT1D specifically has an incidence of 1:1,000,000. (2)
- Primary prevention includes avoidance of prolonged fasting and overexertion, a diet high in carbohydrates and low in fats, and surveillance liver function testing. (7)
- Although fifty cases of CPT1D exist, only one presentation of rhabdomyolysis has been reported in the literature. (4)

Case Report

- History: 18-year-old African American male with mild intermittent, asthma and normal developmental milestones presented to Broward Health Medical Center with complaints of weakness, fatigue, and bilateral leg cramping. He has a history of five episodes of rhabdomyolysis starting from age 8, precipitated by viral infections including coxsackie B, adenovirus, influenza B, and parainfluenza-3. During this admission, patient denied overexertion, viral prodrome, and trauma, but did endorse skipping meals. He admits to mild nausea and diffuse generalized body aches. He reports his urine being tea-colored. He denied use of new prescription medications or over the counter herbs and supplements. He also denied alcohol, tobacco, and illicit drug use. He denied any chest pain, palpitations, shortness of breath, abdominal pain, vomiting, diarrhea, diaphoresis, fever, chills, and headache.

- Vital signs: Within normal limits
- Physical exam: Bilateral lower extremity tenderness to palpation

- Labs:
  - CK initial > 42,000
  - Electrolyte abnormalities consistent with severe rhabdomyolysis.
  - Urinalysis showed myoglobinuria.
  - Viral panel was negative.
  - Urine drug screen was negative

Hospital Course

- CK levels trended upward and peaked at over 1.17 million (Figure 2).
- Mycoplasma IgM found to be positive.
- Muscle biopsy of right thigh revealed severe myopathy consistent with rhabdomyolysis.
- Quantitative plasma acylcarnitine studies showed elevated C2-C6 and C14 in the absence of carnitine supplementation.
- Urine organic acid quantification demonstrated elevated methylsuccinic acid (5.0). (Figure 2)
- On chart review in 2016, both free and total carnitine levels were markedly elevated.
- Patient continued to complain of leg cramping
- Vital signs and clinic presentation remained stable overall.
- Treatment course: hemodialysis, fluid resuscitation for ARF. Recommended to adhere to diet high in carbohydrates, lower in fats, and not to undergo time periods of extended fasting overexertion. Instructed to undergo genetic testing on discharge

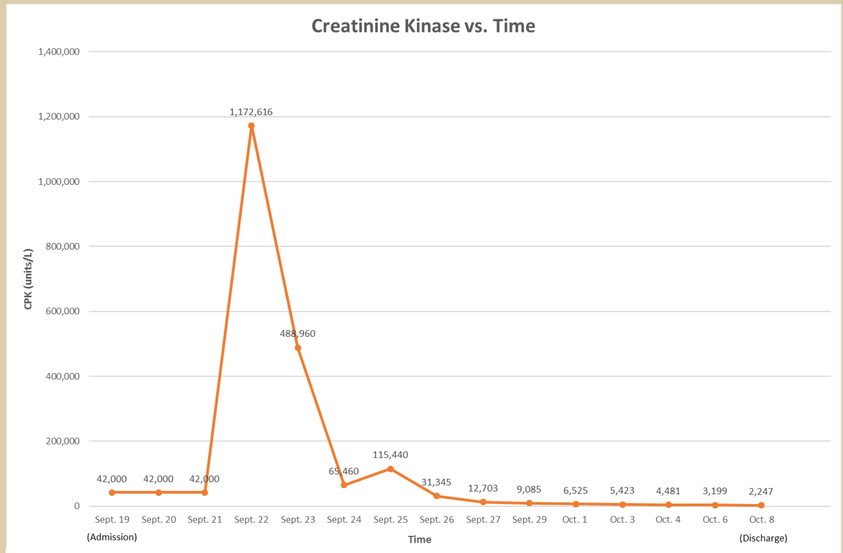

Fig. 1

Disorder	Primary Acylcarnitine Biomarkers	Other Acylcarnitine Abnormalities	Primary Organic Acid Biomarkers	Other Biomarkers
Carnitine uptake defect	↓ C0; very low free carnitine	↓ Total carnitine	NA	↓ Glucose and ketones (fasting); ↑ CK
Carnitine/acylcarnitine translocase	↑ C16; ↑ C18; ↑ C18:1	↑ C18:2; ↑ C14; ↓ Carnitine	NA	↑ NH_4; ↑ transaminases; ↓ Glucose, ketones (fasting)
Carnitine palmitoyltransferase 1	↑ C0; ↓ C16; ↓ C18; ↑ C0/(C16 + C18)	↓ Overall acylcarnitines	NA	↓ Glucose, ketones (fasting) ↑ NH_4
Carnitine palmitoyltransferase 2	↑ C16; ↑ C18; ↑ C18:1	↑ C16:1; ↑ C18:2; ↑ C14:1; ↑ C14	NA	↑↑ CK, ↑ myoglobin in urine
Very long-chain acyl-CoA dehydrogenase	↑ C14:1; ↑ C14:2	↑ C14; ↑ C16; ↑ C18:1, ↑ C18:2	NA	↑ NH_4, ↑↑ CK, ↑ myoglobin in urine ↓ Glucose and ketones (fasting)
Medium-chain acyl-CoA dehydrogenase	↑ C8; ↑ C10:1; ↑ C10	↑ C6	Hexanoylglycine, suberylglycine Dicarboxylic acids	
Short-chain acyl-CoA dehydrogenase	↑ C4		Ethylmalonic acid, methylsuccinic acid, butyrylglycine	
Long-chain L-3-hydroxyacyl-CoA dehydrogenase/ mitochondrial trifunctional protein	↑ C16-OH; ↑ C18-OH; ↑ C18:1-OH		C10 to C14 3-hydroxy-dicarboxylic acids	↑ Long-chain serum 3-OH-fatty acids; ↑ NH_4
Medium/short-chain L-3-hydroxyacyl-CoA dehydrogenase	↑ C4-OH		3-OH-glutarate	↑ Medium/short-chain serum 3-OH-fatty acids serum; ↑ insulin
Multiple acyl-CoA dehydrogenase	↑ C5; ↑ C5-DC; ↑ C8; ↑ C14:1	↑ C4-C8	Glutaric acid, ethylmalonic acid, many acylglycines (isovaleryl, hexanoyl, suberyl, isobutyryl, butyrl, 2-methylbutyryl); dicarboxylic acids	↓ Glucose and ketones (fasting)

Fig. 2

Discussion

- This is a very unique case of rhabdomyolysis with a peak CK of approximately 1.2 million.
- Our patient demonstrated elevated free and total carnitine levels, elevated C2-C5, relative hypoglycemia with urine organic acids devoid of ketones, and an elevated ratio of C0 to the sum of C16 and C18.
  - Findings are all consistent with NIH diagnostic criteria for CPT1D. (2)
- Although adult onset recurrent rhabdomyolysis is more commonly associated with CPT2D, lack of C16, C18, C18:1 make this less likely. (3,12)
- Although elevated C4 and urine methylsuccinic acid is associated with short chain acyl-coA dehydrogenase, lack of ethylmalonic acid, methylmalonic acid, and high total carnitine, make this diagnosis less likely as well. (11) (Figure 2)
- In 2018, prior genetic testing revealed GAA intronic heterozygous mutation and whole exome sequencing revealed NEB heterozygous mutation suggesting Pompe's and Nemaline Myopathy, respectively. (6,9)
  - However, these disorders are known to have multiple comorbidities not present in our patient.
- Additionally, muscle biopsy failed to report nemaline bodies.
- In conclusion, we present the second case of late onset rhabdomyolysis due to presumed CPT1D.
- Recent studies have uncovered 3 subtypes of CPT1D including liver isoform (CPT1a), muscle isoform (CPT1b), and neuronal isoform (CPT1c).
  - CPT1a deficiency are the only human cases reported.
- Pending specialized genetic, we may have discovered the first case of CPT1b deficiency.
- Until then, it remains unclear whether the lack of CPT1b cases is due to embryonic demise, as seen in CPT1b knockout mice, or from extremely low incidence. (2,10)

Conclusion

- This case report demonstrates a rare presentation of recurrent rhabdomyolysis secondary to potentially rare fatty acid oxidation disorder reported in the human population.
- We found fifty cases of CPT1D in the literature. (4)
  - However, only one presentation of rhabdomyolysis has been reported.
- Further, CPT1D should be taken into account in differential diagnosis of recurrent rhabdomyolysis. A high index of suspicion is needed.

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