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Case Report

Recurrent rhabdomyolysis caused by carnitine palmitoyltransferase II deficiency, common but under-recognised: Lessons to be learnt



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ABSTRACT

We discuss two adult siblings who presented with symptoms of myalgia and rhabdomyolysis following exercise with myoglobinuria; genetic testing confirmed carnitine palmitoyltransferase II deficiency and resulted in institution of appropriate crisis management and dietary advice. We explore the phenotypic variability of this commonest fatty oxidation defect that remains under-diagnosed in the adult population and provide clues for early recognition and diagnosis.

1. History

The index patient was a 35-year old woman with a longstanding history of tiredness after exercise since 12 years of age. She joined the army aged 18-years of age and served for 12 years. During this period, she noted frequent episodes of muscle aches, weakness and dark urine following vigorous exercise. Her older brother aged 40-years was asymptomatic until recently; however, following a dental procedure under local anaesthetic (Lidocaine 1%), he developed episodes of severe tiredness, muscle cramps associated with dark urine and was also investigated further.

2. Examination

Both the siblings were well grown with normal neurological examinations.

3. Investigations

The index patient was noted to have an elevated creatine kinase as high as 68,000 IU/L on one occasion and myoglobinuria. Plasma acylcarnitine analysis showed increases in C16 and C18 species with normal free carnitine. The brother also showed slightly elevated CK at 348 IU/L with a similar plasma acylcarnitine profile.

In index patient: Plasma acylcarnitine profile. Increased

concentration of the following acylcarnitines ($\mu\text{mol/L}$):

C0 = 27 (ref 15–53)
C2 = 7.44 (ref 5–27)
C16:1 = 0.19 (ref < 0.08)
C16 = 0.86 (ref < 0.24)
C18:1 = 1.50 (ref < 0.28)
C18 = 0.34 (< 0.10)
Normal free carnitine [*i.e.* C0] 27 $\mu\text{mol/L}$ (ref 15–53).

In older sibling: Plasma acylcarnitine profile:

C0 = 30.81 (ref 15–53)
C2 = 8.84 (ref 5–27)
C16:1 = 0.04 (ref < 0.08)
C16 = 0.56 $\mu\text{mol/L}$ (ref < 0.24)
C18:1 = 0.71 (ref < 0.28)
C18 = 0.31 (< 0.10)
Normal free carnitine [C0] 31 $\mu\text{mol/L}$ (ref 15–53).

4. Molecular testing

Genetic testing was undertaken at Sheffield Diagnostic Genetics Service, initially in the sister's genomic DNA, through targeted Sanger sequencing for the two common pathogenic variants in *PYGM*:

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c.148C > T, p.Arg50* and c.613G > A, p.Gly205Ser associated with Glycogen storage disease type V (McArdle disease). Subsequent testing showed she was heterozygous for the common c.338C > T, p.Ser113Leu pathogenic variant in exon 3 of *CPT2*, and extended mutation screening then identified a second, novel c.1665C > G, p.His555Gln likely pathogenic variant, affecting a highly conserved amino acid position among acyltransferases, and supported by variant effect prediction software programs. This variant was not present in population databases. Carrier testing of parents confirmed that this patient was a compound heterozygote. These results confirmed the clinical diagnosis of CPT II deficiency. Testing in the brother also showed that he carried both these variants in *CPT2*.

5. Management

Following genetic diagnosis, both siblings were referred to the metabolic service for management of their symptoms and dietary advice. Advice was provided regarding avoidance of fasting, excessive exercise, modest dietary fat restriction and prescription of medium chain triglycerides (Vitaflor MCT Procal) and Vitaflor SOS25 for emergency use. An emergency regimen (www.bimdg.org.uk) was provided for management of acute crises. Advice was also provided regarding avoidance of medications including non-steroidal anti-inflammatory drugs (especially ibuprofen for post-exercise muscle pain as this may increase the likelihood of renal failure), seeking specialist advice prior to general anaesthetic use; annual flu vaccinations.

6. Outcome

For these siblings who presented with the late myopathic form of CPT II deficiency, it has been crucial to make the correct diagnosis in order to institute appropriate management.

7. Discussion

Carnitine palmitoyltransferase II deficiency (CPT II deficiency) is a long-chain fatty-acid oxidation disorder and consists of three different clinical presentations: a lethal neonatal form, severe infantile form and a more common myopathic form (which can be mild with manifestations from infancy to adulthood) [2]. The two severe forms have multi-system involvement with liver failure, cardiomyopathy, seizures and early lethality. The focus of this discussion is the milder, myopathic form of CPT II deficiency which is the most common disorder of lipid metabolism affecting skeletal muscle but remains under-diagnosed due to lack of understanding of its clinical presentation [Wieser et al. 6] Genereview: <https://www.ncbi.nlm.nih.gov/books/NBK1253/>.

The myopathic form of CPT II deficiency should be suspected in individuals presenting with recurrent attacks of muscle weakness and myoglobinuria precipitated by certain drugs, prolonged exercise, and episodes of fasting or stress [4]. They may also present with weakness during such crises but generally there are no intercurrent signs of myopathy. Males generally tend to be more severely affected than females. There is usually a more than five-fold increase in serum CK levels with elevation of C12 to C18 acylcarnitine on measurement of plasma acylcarnitines.

Confirmatory diagnosis is by identification of disease-causing variants in *CPT2* through targeted testing [1]. In terms of genotype-phenotype correlation, missense pathogenic variants cause the myopathic form with p.Ser113Leu accounting for 60% of pathogenic variants in

this form of the condition [5]. *CPT2* pathogenic variants that result in truncation of protein or mRNA degradation are more likely to be associated with the severe forms of the condition [6].

In this family, following identification of the common pathogenic p.Ser113Leu variant, extended screening identified the second, previously unreported variant: p.His555Gln; this variant affects a highly conserved amino acid; *in silico* analysis supports pathogenicity and not present in population databases.

The myopathic form of CPT II deficiency is the commonest fatty acid oxidation disorder affecting muscle and the one most likely to cause myoglobinuria. Consequently, if the clinical history includes “unexplained” rhabdomyolysis, clinicians should have a low threshold to perform plasma acylcarnitine analysis as a first line investigation, especially in the context of elevated CK. If this is suggestive, it is important to obtain confirmatory genetic diagnosis as this informs management of this under-recognised condition. It is also important as heterozygotes have occasionally been reported with a clinical phenotype, although they are more likely to only have a biochemical phenotype [3].

Management of myopathic CPT II deficiency is mainly focused on preventing renal failure during a crisis and involves avoidance of known triggers, reducing dietary long-chain fats, providing carnitine and adequate hydration. It is important that these individuals have specialist dietary advice and annual monitoring.

Author contributions

All authors contributed to and approved final manuscript; MB: clinical phenotyping; genetics and writing manuscript; RJK, IMN: Genetic analyses; TMJ: neurological and clinical work-up; GTG, MH, SEO: metabolic work-up and advice.

Conflicts of interest

None to declare for all authors.

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