

A 36-year-old male with episodes of exercise-induced rhabdomyolysis: the importance of exercise testing and muscle biopsy for mitochondrial myopathies

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This case has been previously presented at the virtual 44th Annual Carrell-Krusen Neuromuscular Symposium in Dallas, Texas held from February 24-25, 2022.

Introduction

The differential for recurrent exercise-induced rhabdomyolysis is broad and includes, amongst many other conditions, metabolic myopathies and mitochondrial disorders. While metabolic and mitochondrial diseases can be challenging to confirm, given the episodic nature or non-specific symptoms, mitochondrial myopathies are particularly challenging because of the clinicopathologic heterogeneity. This case illustrates the importance of exercise testing and muscle biopsy in evaluating patients with suspected mitochondrial myopathies.

Mitochondria possess proteins from nuclear DNA (nDNA) and mitochondrial DNA (mtDNA), maternally inherited latter. Since some of the mitochondrial proteins are encoded by nuclear genes, inheritance for these nuclear genes follows Mendelian patterns^{1,2}. Diagnosis of these conditions is complicated by the numerous genes (approximately 1500 genes encoded in both mitochondrial and nuclear DNA) that do not have clear genotype-phenotype correlates^{1,3}. Variability is partly attributable to varying heteroplasmy levels between family members and even within different tissue types in a single person¹.

Mitochondrial myopathies may have systemic complications, but symptoms can be isolated to muscle and exercise intolerance. The physical exam can be normal outside of systemic symptoms (e.g., hearing or vision loss, ptosis, or ophthalmoplegia) related to mitochondrial

myopathies. Laboratory findings, such as elevated creatine kinase (CK) or lactic acid values, are nonspecific and can be normal, with suspicion of a metabolic myopathy likely to arise from the appropriate clinical history³. Multiple testing modalities may be needed to confirm the diagnosis of mitochondrial myopathy.

Case Report

History

A 36-year-old man with a history of migraines was referred to the neuromuscular clinic for unexplained episodes of exertional rhabdomyolysis. He was lifting weights approximately three years before his visit. He then had an episode of pain, weakness, and edema in his upper arms with an elevated CK, which was diagnosed as rhabdomyolysis. Before that, he was healthy and athletic. He was a competitive athlete and was doing well in sports though he had difficulty with long-distance sports. He was able to lift heavy weights without difficulty. Since then, he has had four total episodes of rhabdomyolysis. He described cramps that were more prominent than myalgias. He had no change in his exercise tolerance with glucose intake before exercise. He had no worsening of muscle symptoms with fasting or fevers. He denied contractures or transient contractures. He also denied dyspnea, dysphagia, and diplopia. Notably, he had prominent fatigue after longer workouts. He could complete his workouts and was not limited to short bursts of exercise like lifting or sprinting; however, he could not engage in continuous, prolonged exercise.

He has a history of hypertension, a cholecystectomy, and two lumbar decompression surgeries. He has three daughters that are all healthy. One maternal nephew has ptosis. There is no sudden cardiac death in the family. He denied current tobacco, alcohol, or drug use. He had no known drug allergies. He takes lisinopril, coenzyme Q10 (CoQ10), and a multivitamin daily.

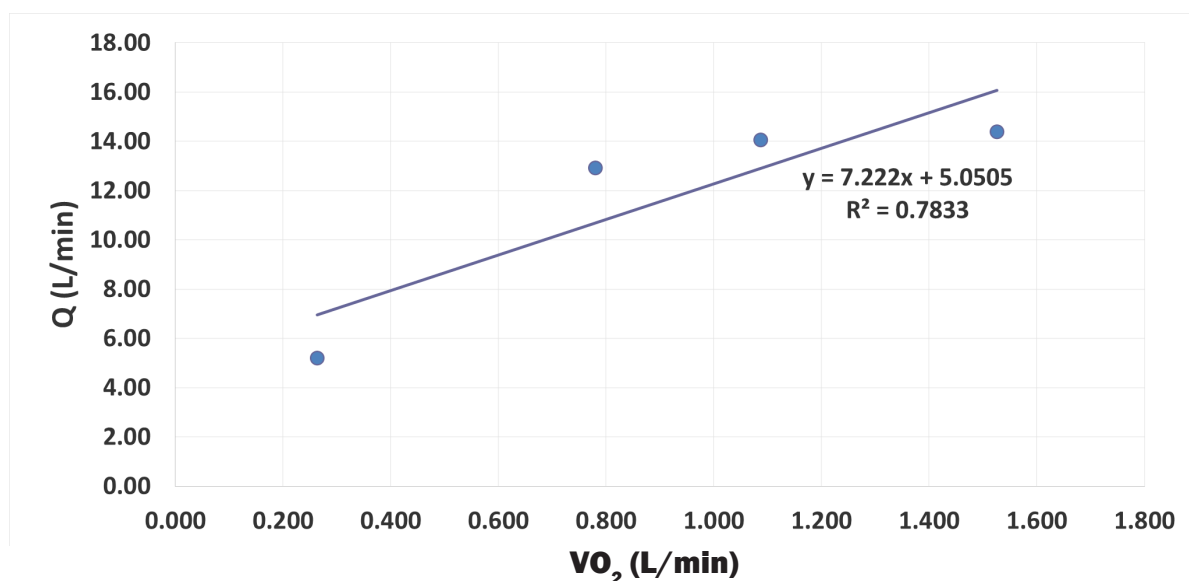
Physical

His exam was nearly normal except for his cranial nerves, where he had bilaterally limited abduction, left worse than right. He also had left non-fatigable ptosis. Otherwise, his cranial nerves, muscle strength, sensation, reflexes, coordination, and gait were normal.

Diagnostic testing

Prior laboratory workup was notable for normal baseline CK, total and free carnitine, non-fasting acylcarnitine profile, and lactic acid. Additional studies, including hemoglobin A1c, methylmalonic acid, cobalamin, antinuclear antibodies, serum protein electrophoresis

Figure 1: Aerobic exercise test



$$\frac{\Delta Q}{\Delta VO_2}$$

Q: cardiac output, VO₂: volume of oxygen consumption. The ratio between cardiac output and oxygen consumption ($\frac{\Delta Q}{\Delta VO_2}$) is 7.222, suggestive of a defect in oxidative phosphorylation.

with immunofixation, serum-free light chain, erythrocyte sedimentation rate, thyroid stimulating hormone, basic metabolic panel, complete blood count, and syphilis were unremarkable. He had a normal MRI of bilateral thighs with contrast, including no fatty replacement or abnormal signal. Electromyography (EMG) revealed mild chronic non-irritative proximal myopathy, and the nerve conduction study was normal. His Invitae limb-girdle muscular dystrophy and GeneDx metabolic myopathy gene testing panel did not reveal a pathogenic mutation. The patient had mtDNA gene testing via buccal swab testing that revealed a DNA polymerase gamma (*POLG*) c.2642 C>T heterozygous variant of unknown significance (VUS) and did not reveal any mutations in the mtDNA. The Provean score was -9.89, with conflicting interpretations of pathogenicity.

Given his clinical picture, there was suspicion of mitochondrial myopathy. He had an aerobic cycle exercise test with a ramp protocol. His cycle exercise test showed a peak exercise heart rate of 171 bpm, 93% of his predicted maximal heart rate. The patient's perceived exertion was of maximal effort (19/20 rated perceived exertion and 9/10 leg exertion scales), with general and leg fatigue symptoms. Peak oxygen consumption (VO₂ max) was 24.4 ml/kg/min, and the predicted VO₂ max was 26.1 ml/kg/min, below average for age and sex. Cardiac output (Q) was within normal limits at rest but was exaggerated during exercise with respect to oxygen utilization. There was a blunted peak arteriovenous oxygen difference at peak exercise (a-vO₂).

Lactate was normal at rest and during exercise, with normal elevations post-exercise. The change in cardiac output relative to VO₂ was 7.22 (Figure 1).

These results suggest an oxidative defect; thus, a muscle biopsy was pursued to assess his mitochondria. Muscle biopsy mtDNA analysis revealed multiple deletions of the mitochondrial genome (13 kilobase (kb) deletion m.3264_16071del12808 and 12 kb deletion m.3578_15546del11969, the entirety of the mtDNA is 16.6 kb). Interestingly, his muscle's histochemical analysis and electron microscopy did not reveal any changes suggesting a mitochondrial myopathy.

Based on the cycle exercise testing (Figure 1) and muscle biopsy mtDNA analysis results, the diagnosis was consistent with mitochondrial myopathy. Given the multiple deletions, this is consistent with the *POLG* mutation, which was reclassified to likely pathogenic. He was given the clinical diagnosis of chronic progressive external ophthalmoplegia (CPEO).

Discussion

This case emphasizes the importance of tissue-specific testing in cases where prior blood or buccal testing is inconclusive. Additionally, exercise testing can help identify defects in oxidative phosphorylation, which can support a diagnosis of mitochondrial myopathy and help resolve unclear genetic findings. There can be reduced VO₂ max, reduced peripheral oxygen extraction (a-vO₂), and hyperkinetic circulation (elevated baseline

cardiac output)^{3,5}. In a study of 40 patients with primary mitochondrial disease (PMD), the capacity to increase oxygen extraction during exercise was severely attenuated in the PMD group, as indicated by a low peak systemic a-vO₂ difference compared with healthy subjects⁵. Care must be taken when interpreting exercise tests, as several factors can alter the results, including a submaximal effort.

Next-generation sequencing (NGS) of DNA can be useful⁶. Although NGS is useful when pathogenic variants are found, variants of unknown significance are common, particularly in mitochondrial myopathies³. Unlike mutations in nuclear-encoded genes, the proportion of mtDNA copies containing a mutation can vary widely between different cells in the same individual¹. While serum and buccal samples are sensitive to point mutations in mtDNA, there is greater sensitivity for deletions and duplications in muscle tissue, and mutations may only be present in specific tissues due to heteroplasmy (e.g., no mutations in leukocyte and buccal samples with a mutation in muscle)⁶. Thus, muscle biopsy can be used to identify mimics or perform enzyme or respiratory analysis in addition to performing mtDNA analysis.

Diagnosis of mitochondrial myopathies may require multiple testing modalities, including exercise testing, muscle pathology, enzyme or respiratory analysis, and molecular testing, as false negatives are common. Analysis of mtDNA has rapidly expanded in the last 30 years and is particularly useful in cases with high suspicion of disease, mainly when supported by exercise physiology data⁶. Data

from performance on exercise testing and findings on muscle biopsy (multiple mitochondrial DNA deletions in this case) are essential for reclassifying variants of unknown significance as a pathogenic mutation.

References

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