Rhabdomyolysis and exercise intolerance in a 45-year-old man

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ABSTRACT
A 45-year-old man presented to neuromuscular clinic after a first-time episode of non-traumatic rhabdomyolysis after aerobic exercise. Prior to his diagnosis, he had an extensive medical workup to evaluate for elevated transaminases and creatinine, including liver and renal biopsies. On history, the patient confirmed a lifelong history of exercise intolerance. Creatine kinase evaluation revealed an elevated baseline value. Genetic testing disclosed homozygous variants of uncertain significance and required exercise testing and muscle biopsy to identify the underlying etiology. This case demonstrates pitfalls of genetic testing and an approach to identify this form of myopathy.

Section 1

A 45-year-old man presented to neuromuscular clinic for an episode of non-traumatic rhabdomyolysis. He had a history of elevated transaminases for which he underwent two liver biopsies, seven years and one year prior to his clinic visit, and was diagnosed with fatty liver disease. He was noted to have an elevated creatine kinase (CK) to the 3800s U/L after his second liver biopsy. He had repeat CK values that were elevated but less than 1000 U/L. After performing routine aerobic exercise, he developed muscle weakness and dark colored urine. He was admitted for further work-up. CK was >35,000 U/L and creatinine (Cr) peaked at 6.66. A renal biopsy was performed and was normal. His CK and Cr improved with intravenous fluids. MRI of his proximal lower limbs and EMG were normal. During his initial clinic visit, he described difficulty with exercise since childhood. He had no prior identifiable episodes of rhabdomyolysis or myoglobinuria. He denied weakness, cramping, contractures, rashes, dyspnea, and dysphagia. There was no family history of muscle or metabolic disorders. The neurological exam was normal. There were no rashes and lungs were clear to auscultation bilaterally.

Questions for consideration:

1. What diagnoses should be considered?
2. What tests would you perform next?

Section 2

The patient's symptoms localize to the muscles given the elevated CK and rhabdomyolysis. Normal EMG and strength exam do not eliminate a myopathy from the differential. The patient's reported persistent exercise difficulty since childhood and rhabdomyolysis were most suggestive of a metabolic (glycolysis/glycogenolysis and fatty acid oxidation disorders) or mitochondrial myopathy. Typically, glycogen-storage disorders present during periods of high-intensity exercise, whereas fatty acid oxidation disorders and mitochondrial myopathies present during longer duration endurance-type activities or periods of metabolic stress such as surgery or infection. Given the non-specific history of exercise intolerance, further investigation was needed to differentiate between these. There were no systemic features which could point to a specific subtype of fatty acid oxidation disorder. There were no specific features such as proximal weakness or a rash that would suggest an inflammatory myopathy. The patient was not taking statins or cortico- or anabolic steroids, which excluded forms of drug-induced myopathy.

Comprehensive testing was performed to narrow the diagnosis. Repeat CK was 609 U/L. A neuromuscular disorders gene panel (Invitae, next-generation sequencing) was obtained and revealed a pseudodeficiency allele in *GAA* and homozygous variant of uncertain significance in *PYGM* (c.403G>A [p.Gly135Arg]). Non-ischemic forearm test (NIFT) (Table 1A) and cycle exercise test (Table 1B) were performed. Cycle exercise test showed elevated heart rate (HR) and rate of perceived exertion (RPE) at low workloads with a reduction of HR (31 beats per minute from minute 8 to 16) and RPE with better tolerance to higher workloads, a physiologic response known as the second wind phenomenon, seen in McArdle disease (GSD V).

Table 1

A. Non-ischemic forearm test

Time	Absolute Force (kg)	Grip Force (% max)	Lactate mM	Ammonia µM/L	Serum CK
rest	30.0	100	0.67	31	1834
1 sec	15.6	52			
30 sec	19.4	65			
60 sec	12.9	43	0.68	97	
post exer					
1 min			0.41	121	
2 min			0.46	74	
5 min			0.55	41	
10 min			0.56	34	

Lactate response was blunted, and ammonia production was increased in the context of a baseline elevated CK value.

B. Cycle exercise test

Time (min)	WL (watts)	RPE Overall	O_2 sat. (%)	BP (mmHg/mmHg)	HR (bpm)	VO_2 (L/min)	Q (L/min)	a-vO_2diff (mlO_2/dlQ)	ΔQ/ ΔVO_2	lactate (mM)
0	rest		98	130/98	78	0.376	5.97	6.3		0.63
1	10	11	98	181/107	112					
2	20	12	98	166/92	119					
3	30	14	98		125					
4	30		98		135					
5	30	16	99	196/93	145	1.180	19.07	6.2		0.40
6	30									
7	30	16	98		156					
8	20	17	98		162					
9	20	15	97							
10	20	14	97	192/91	155					
11	20	14	97		150					
12	20	13	97	169/92	142					
13	20	13	97		136					
14	20	13	97		133					
15	20	13	96	181/85	132	1.533	14.81	10.4		0.51
16	30	13	96		131					
17	30	14	97		134					
18	40	15	97	174/96	136					
19	50	14	98		146					
20	60				148					
21	70	16	98	187/91	153					
22	70	17	97		162					
23	70	17	97	209/83	165	2.010	18.67	10.8	7.29	0.42

The exercise test showed reduced peak VO_2, blunted lactate production, second wind phenomenon, and a defect in oxidative phosphorylation.

WL: workload, RPE: Rate of Perceived Exertion (6-20, no exertion to maximal exertion), BP: blood pressure, HR: heart rate, VO_2: oxygen consumption, Q: cardiac output, a-vO_2 diff: arteriovenous oxygen difference

Questions for consideration:

1. What additional testing would you obtain to determine the diagnosis?

Section 3

A lifetime of exercise intolerance, non-traumatic rhabdomyolysis, and chronically elevated muscle enzymes are all highly suggestive of a metabolic myopathy. While primary mitochondrial myopathies (PMM) and fatty acid oxidation disorders (FAOD) can present with exercise intolerance and rhabdomyolysis, the lack of lactate production on NIFT and the second wind phenomenon argue in favor of a glycogen storage disorder (GSD), specifically McArdle disease. His genetic results and absence of symptoms with fasting, illness, and exposure to cold temperatures argue against FAOD and mitochondrial myopathies. It is therefore unnecessary to order mitochondrial DNA testing or urine organic acids, serum acylcarnitine, and carnitine profiles. We pursued a vastus lateralis muscle biopsy to test for the defective enzyme in GSD V, myophosphorylase (PYGM gene). The patient's myofibers revealed a complete absence of reactivity (Figure 1) and provided the diagnosis. His homozygous VUS was recharacterized as pathogenic per American College of

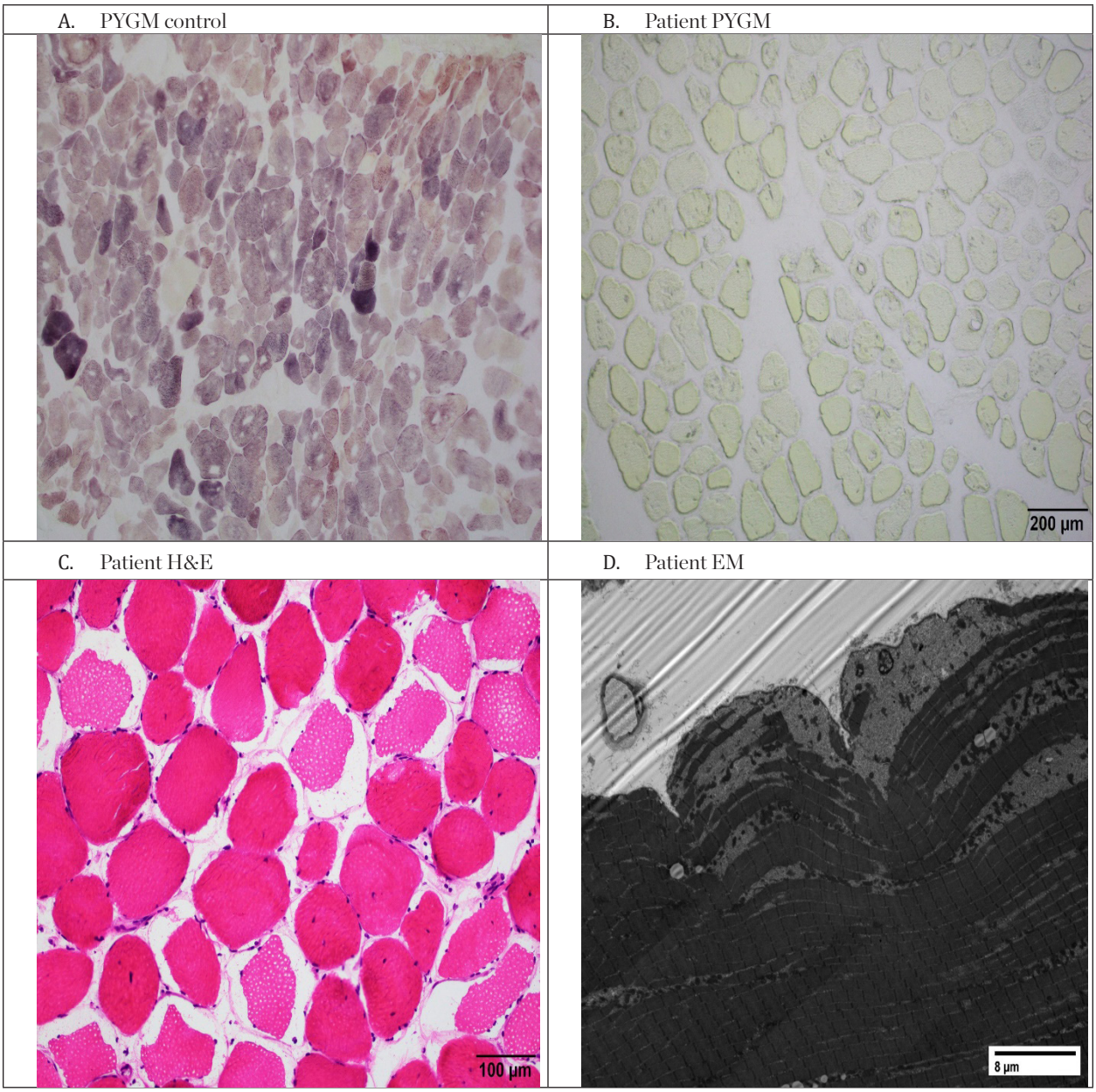

Figure 1: Quadriceps muscle biopsy showed a vacuolar myopathy with subsarcolemmal vacuoles (arrows) in a subset of myofibers (C), complete absence of myophosphorylase reactivity in all myofibers (B) compared to a control myophosphorylase image (A), and accumulation of free glycogen particles in subsarcolemmal space in some fibers on EM (D). Periodic acid-Schiff is not shown as there was no increased PAS staining.

Medical Genetics and Genomics guidelines given the low frequency of this mutation in the population, established clinical testing, and *in silico* analysis.

The patient was educated on the second wind phenomenon, benefits of high carbohydrate diet, and high-risk activities that could trigger rhabdomyolysis. We recommended low and moderate intensity aerobic exercises with modest use of sports drinks prior to activity. After implementing these measures, he reported an improvement in muscle symptoms and has not had a recurrence of rhabdomyolysis.

Discussion

McArdle disease[1] is an autosomal recessive disorder caused by a *PYGM* gene defect, encoding for myophosphorylase, a muscle-specific isoform of glycogen phosphorylase that catalyzes the degradation of glycogen into glucose-1-phosphate. Nearly all mutations in *PYGM* lead to complete loss of enzyme activity, thus blocking glycogenolysis.[2,3] In the initial stages of exercise and during intense activities, skeletal muscle predominantly depends on anaerobic glycogenolysis for energy. Thus, within minutes of starting the activity, patients describe fatigue that progresses to muscle cramps, contractures, and rhabdomyolysis if the activity is continued. Since glycogen is also needed for oxidative metabolism, patients have a low capacity for moderate exercise as well. Sustained moderate activity leads to fatigue, tachycardia, and dyspnea. After resting or maintaining a low level of activity, patients experience the pathognomonic second wind phenomenon related to greater mobilization of fatty acids to fuel oxidative metabolism.[4,5,6]

Although exercise intolerance is present in childhood, the diagnosis is almost never made until at least the second decade of life due to misdiagnoses like "growing pains" or "being unfit." Patients typically present in early adulthood with exercise intolerance, cramps, and recurrent rhabdomyolysis that can progress to fixed proximal weakness.[1] Work-up often begins at the time of non-traumatic rhabdomyolysis. CK is typically elevated to 5-10 times the upper limit of normal. Importantly, AST and ALT are present in myofibers and are not specific for liver pathology and can lead to unnecessary invasive procedures, such as liver biopsy. Significant delays in diagnosis are common, with a high rate of misdiagnosis (up to 90%). Women are substantially more likely to receive a psychiatric or psychological misdiagnosis.[6]

NIFT is classically performed rather than ischemic forearm testing, which can lead to muscle contractures and rhabdomyolysis.[7,8] During NIFT, a block in glycogenolysis is demonstrated by absent lactate and increased ammonia production. Cycle testing demonstrates and helps patients recognize the second wind phenomenon. Molecular testing may obviate the need for exercise testing and muscle biopsy in patients with the typical clinical phenotype and known pathogenic *PYGM* mutations. When *PYGM* VUS are found, a normal NIFT can exclude GSDs. If NIFT is abnormal, a muscle biopsy should be performed to assess for myophosphorylase activity.

The goal of management is to reduce episodes of rhabdomyolysis and improve exercise tolerance. Avoidance of intense activities, especially those requiring isometric, repetitive, and eccentric actions, is recommended. Low-to-moderate aerobic exercise (no greater than approximately 70% of maximal HR) improves muscle oxidative capacity and increases the threshold for muscle injury due to exertion.[9] Patients should warm-up at a low intensity for at least 10 minutes to help achieve the second wind phenomenon. Pre-exercise simple sugars improve exercise tolerance and reduce the risk of rhabdomyolysis during activity.[10-12] Because McArdle disease patients are at risk of obesity, consuming sugar prior to all activity is not recommended. Additionally, carbohydrate-rich diets are beneficial by bolstering hepatic glycogen stores and glucose mobilization.

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