Unraveling the culprit behind the exercise-induced recurrent rhabdomyolysis in a young adult

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Abstract

Background: *Recurrent rhabdomyolysis induced by exercise or physical exertion in a healthy young individual is uncommon and necessitates further investigations of an underlying disorder. Metabolic myopathy is one of the rare causes of recurrent rhabdomyolysis in adolescents and adults. Clinical parameters are normal in between the episodes in which patients remain asymptomatic. The acylcarnitine profiles provide a significant clue to diagnosis.*

Case: *We present a case of a young adult female who presented with recurrent exercise-induced rhabdomyolysis. The appropriate diagnosis was established two years after the onset of the first episode of her seemingly uneventful rhabdomyolysis. Her signs and symptoms including her acylcarnitine profile were similar to a long-chain fatty acid oxidation disorder (LC-FAOD). However, genetic analysis showed a missense mutation of RYR1 that has never been reported before. After fatty diet restriction, she has not reported rhabdomyolysis since.*

Conclusion: *Due to the unpredictable nature of symptomatology, the diagnosis and management of metabolic myopathy should be approached carefully. An inconclusive acylcarnitine profile must be confirmed with genetic analysis.*

Keywords: Rhabdomyolysis, acylcarnitine, metabolic myopathy, RYR1

Introduction

Recurrent rhabdomyolysis induced by exercise or physical exertion in a healthy young individual is uncommon and requires additional investigations of an underlying disorder. Metabolic myopathy is one of the rare causes of recurrent rhabdomyolysis in adolescents and adults. Due to phenotypical variability among patients, from lethal illnesses in newborns to exercise-induced rhabdomyolysis in adults, the diagnosis is challenging.[1,2] Clinical parameters are normal in between the episodes in which patients remain asymptomatic. The acylcarnitine profiles provide a significant clue to diagnosis.

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Newborn screening with acylcarnitine profiles as early as 24–48 hours of their birth has been utilized across the United States for metabolic myopathies, with a wide spectrum of diseases in which some individuals may remain asymptomatic during their lifetime.[1,2] We report a case of a previously healthy female who was diagnosed two years later after the first episode of exercise-induced rhabdomyolysis, presumably caused by a fatty acid oxidation disorder (FAOD), with a missense mutation in an *RYR1* gene.

Case

A 21-year-old female presented to an outpatient clinic with recurrent soreness in her proximal upper and lower extremities. She denied a history of autoimmune or myopathies in the family and illicit drug use.

She started having the first episode of muscle soreness following exercise at the age of 18 for which

Table 1. Creatine Kinase, AST, ALT Levels During Her Clinical Course

		Creatinine Kinase (IU/L)	AST (IU/L)	ALT (IU/L)
1st hospital visit	Day 1 (on admission)	11,098	150	36
	Day 2	8,692	96	24
	Day 3	4,851	110	29
	Day 4 (at discharge)	2,294	112	41
1st hospital follow-up	1 week after discharge	213	23	28
	2 weeks after discharge	347	27	16
2nd hospital visit	ER visit	2,506	60	18
2nd hospital follow-up	1 week after ER visit	1,845	–	–
	2 weeks after ER visit	304	28	18
1st established care visit		119	34	31
2nd established care visit		61	17	10

she did not seek medical attention. A year later, she presented to the hospital with increased muscular pain in her biceps and quadriceps after she had had 2 strenuous exercises, lifting heavier weights than usual earlier in the same week. Physical examination revealed mild tenderness along the upper and lower extremity muscles. Her creatinine kinase (CK) level was significantly elevated with increased myoglobin (980 ng/ml) and mild transaminitis (Table 1). Electrolytes including calcium and phosphate levels were normal with no metabolic acidosis; glucose was 73 mg/dl. The hepatitis B antibodies, hepatitis C antibodies, and HIV were non-reactive. Rheumatoid factor, antinuclear antibody (ANA), double-strand antibody, SSA antibody, SSB antibody, anti-proteinase-3, anti-myeloperoxidase, and c-reactive protein were negative. She was treated for rhabdomyolysis with aggressive fluid hydration. The patient was discharged home with advice to avoid heavy physical activities. At a follow-up appointment, her symptoms improved with normal CK levels and liver enzymes.

The following year, she presented to the hospital again due to bilateral lower extremity pain and generalized muscle soreness and weakness for 2 days after resuming her daily workouts over the past week. Her CK level and liver enzymes were elevated (Table 1) without electrolyte derangement. She was referred to a neurology clinic where she had a nerve conduction study (NCS) and muscle biopsy performed. The NCS result was unrevealing while muscle biopsy demonstrated normal muscle fiber glycogen and lipid content with slight denervation atrophy associated with extensive reinnervation.

At our established care appointment, she was asymptomatic. With a clinical history of repetitive exertional rhabdomyolysis, with inflammatory myopathies excluded and non-specific muscle biopsy results, the differential diagnosis was a non-severe form of FAODs. Further investigations with acylcarnitine profiles were summarized in Table 2. Many long-chain acylcarnitine species were elevated suggestive of a long-chain fatty acid oxidation disorder (LC-FAODs). Elevated ketosis (C2) was detected to be related to the patient fasting before the blood test. She was advised on a fatty diet restriction.

At the 3-month follow-up, acylcarnitine profiles were repeated, with improvement in some of the substrate levels (Table 2). The genetic test revealed heterozygous RYR1. C.9364G>A, p.(Val3122Met), which is a variant of uncertain significance (VUS). She complied with the recommendations and has not had symptoms of rhabdomyolysis since.

Discussion

Recurrent rhabdomyolysis with markedly elevated CK level is concerning for some pathological underlying genetic muscle diseases, as the frequency of recurrent episodes is minimal in general.[3,4] Patients

Table 2. Comparison Between Acylcarnitine Species Levels Before and 3 Months After Fatty Diet Restriction

Acylcarnitine Species	Before Fatty Diet Restriction	3 Months After Fatty Diet Restriction
Acetylcarnitine C2	**(H) 17.69**	**(L) 3.46**
Propionylcarnitine C3	0.16	0.21
Iso-/Butrylcarnitine C4	0.10	0.14
Methylmalonylcarnitine C4DC	<0.02	*<0.02
Hydroxybutyrylcarnitine C4-OH	* 0.05	* <0.02
Isovaleryl-/2-Methylbut C5	* 0.06	* 0.06
Tiglyl/Methylcrotonyl C5:1	* <0.02	* <0.02
Glutarylcarnitine C5DC	*** (H) 0.09**	*** 0.02**
Hydroxyisovalerylcarnitine C5-OH	* 0.03	* 0.03
Hexanoylcarnitine C6	* 0.03	* 0.03
Adipoylcarnitine C6DC	* <0.02	* <0.02
Hydroxyhexanoylcarnitine C6-OH	* <0.02	* <0.02
Octanoylcarnitine C8	* 0.43	* 0.04
Octenoylcarnitine C8:1	* 0.07	* 0.04
Suberylcarnitine C8DC	* <0.02	* <0.02
Decanoylcarnitine C10	*** (H) 0.78**	*** 0.08**
Decenoylcarnitine C10:1	* 0.26	* 0.05
Dodecanoylcarnitine C12	*** (H) 0.22**	*** 0.03**
Dodecenoylcarnitine C12:1	*** (H) 0.24**	*** 0.02**
Hydroxydodecanoylcarnitine C12-OH	* 0.02	* <0.02
Tetradecanoylcarnitine C14	*** (H) 0.06**	*** <0.02**
Tetradecenoylcarnitine C14:1	* 0.22	* <0.02
Tetradecadienoylcarnitine C14:2	*** (H) 0.12**	*** <0.02**
Hydroxytetradecanoylcarnitine C14-OH	* <0.02	* <0.02
Hydroxytetradecenoylcarnitine C14:1-OH	*** (H) 0.03**	*** <0.02**
Hexadecanoylcarnitine C16	* 0.14	* 0.05
Hexadecenoylcarnitine C16:1	*** (H) 0.06**	*** <0.02**
Hydroxyhexadecanoylcarnitine C16-OH	* <0.02	* <0.02
Hydroxyhexadecenoyl C16:1-OH	* <0.02	* <0.02
Stearoylcarnitine C18	* 0.05	* 0.02
Oleoylcarnitine C18:1	* 0.19	* 0.04
Linoleoylcarnitine C18:2	* 0.08	* 0.04
Hydroxyoleoylcarnitine C18:1-OH	* <0.02	* <0.02
Hydroxylinoleoylcarnitine C18:2-OH	* <0.02	* <0.02
Malonylcarnitine C3DC	* 0.15	* 0.02

(*continued*)

Table 2. Comparison Between Acylcarnitine Species Levels Before and 3 Months After Fatty Diet Restriction (*Continued*)

Acylcarnitine Species	Before Fatty Diet Restriction	3 Months After Fatty Diet Restriction
Decadienoylcarnitine C10:2	* 0.03	* <0.02
Carnitine Total	* 39	* 41
Carnitine Free	* 19	* 36
Carnitine Esters	*** (H) 20**	*** 5**
Esterified/Free Ratio	*** (H) 1.05**	*** 0.14**

with recurrent episodes should undergo additional investigations.[5] Rhabdomyolysis following exercise or exertion as an isolated episode or recurrent episodes resulting in muscle pain and elevation of CK can be considered normal in some instances.[3] With extensive diagnostic studies, there may be no underlying pathologies identified.[5] A cohort study suggested that patients with CK levels less than 50 times of upper normal limit, no definite muscle swelling or weakness, no myoglobinuria, and without evidence of acute renal failure or electrolyte derangement demonstrated physiological response to exercise.[4]

Diagnostic workup of recurrent rhabdomyolysis should always exclude common etiologies such as muscle trauma, metabolic disturbances, endocrine disorders, or medications. Other causes to be taken into consideration include inflammatory myopathies, muscular dystrophy, or metabolic myopathies.[3] The three main groups of metabolic myopathies: fatty acid β-oxidation disorders, muscle glycogenosis, and mitochondrial diseases, should be especially inspected when other possible causes are excluded.[5] Clinical symptoms, investigations, and muscle biopsies aid in distinguishing the identities–disorders of glycogen metabolism and mitochondrial myopathies can be differentiated by the muscle biopsy findings which showed no glycogen accumulation and ragged red fibers respectively.[3,5] Fatty acid oxidation disorder (FAOD), can be simply screened with glucose level, lactate, and acylcarnitine profile to identify the type of FAOD.[5]

The patient's acylcarnitine profile showed some similarities to LC-FAODs that affect the metabolism of fats greater than 8–12 carbons, caused by a deficit in an enzyme or carrier responsible for the entry of long-chain fats into mitochondria, resulting in the defect of the carnitine cycle and/or the mitochondrial β-oxidation cycle.[2] In this instance, the differential diagnosis includes carnitine palmitoyl-transferase II (CPT II) deficiency, carnitine-acylcarnitine translocase (CACT) deficiency, very long-chain acyl-CoA dehydrogenase (VLCAD deficiency), and long-chain hydroxy acyl-CoA dehydrogenase/trifunctional protein (LCHAD/TFP) deficiency.[1,2]

The diagnosis is challenging as LC-FAODs clinical parameters i.e. CK, return to normal when patients are asymptomatic.[1] The acylcarnitine analysis allows the identification and differentiation of each LC-FAOD in symptomatic or asymptomatic patients and is used as a screening test in newborns before the development of symptoms.[1] The most accurate acylcarnitine profiles should be obtained during the episode of symptoms. Additional investigation with genetic analysis is a confirmation of the definite diagnosis.[1,2] The genetic analysis of this patient revealed a heterogenous missense variant, heterozygous RYR1. C.9364G>A, p.(Val3122Met), which has not been reported in any medical literature or on the disease-variation database.

RYR1 (ryonadine-receptor 1) gene encodes a calcium iron channel in sarcoplasmic reticulum of skeletal muscle. Its mutation contributes to a spectrum of congenital myopathies or RYR1-related myopathies.[6] Clinical signs and symptoms usually present at a young age with abnormal muscle biopsies which do not align with our patient's.[6,7] We postulated that the missense mutation in this patient contributed to a novel mutation in an LC-FAOD or merely a co-incidental in idiopathic rhabdomyolysis. However given her clinical remission with fatty diet restriction, the diagnosis of LC-FAOD is more likely the cause of her symptoms.

How much long-chain fatty acids should be limited is dependent upon the individual's gene mutation and

disease activity and supplement with medium-chain triglycerides to bypass the oxidation process of long-chain fatty acids.[1,2] In adults, a reduction of calories from fat to 30–35% of total energy is appropriate if there is no severe disease.[1] Mild-moderate forms typically experience intermittent symptoms when β-oxidation activity or lipolysis increases such as in fasting or endurance-type exercise.[1,2] During sick days, patients should be advised to increase fluid and caloric intake to prevent catalysis.[1,2] In hospitalized patients, the maintenance of caloric intake to suppress catabolism is manageable with intravenous dextrose and/or enteral feeds.[1]

Conclusion

Recurrent rhabdomyolysis is concerning for a pathological underlying genetic muscle disease and is worth investigating for, in order to prevent future episodes. Due to the unpredictable nature of symptomatology, the diagnosis and management of FAODs are challenging. The key to diagnosis is acylcarnitine profiles which are best performed during the episode of symptoms. The definitive diagnosis is confirmed with genetic analysis. With extensive investigation, the recurrent rhabdomyolysis can be idiopathic.

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