Importance of acylcarnitine profile analysis for disorders of lipid metabolism in adolescent patients with recurrent rhabdomyolysis: Report of two cases

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Abstract

Metabolic myopathies due to disorders of lipid metabolism are a heterogeneous group of diseases. Newborns may present with hypotonia and convulsions, while progressive proximal muscle weakness or recurrent episodes of muscle weakness accompanied by rhabdomyolysis/myoglobinuria may be seen in older ages. There is little knowledge on detection of disorders of lipid metabolism by acylcarnitine profile (ACP) analysis by tandem mass spectrometry outside the neonatal period particularly in cases with recurrent rhabdomyolysis first presenting in adolescence and adulthood. Two adolescent female cases presented with episodes of rhabdomyolysis and muscle weakness. A 13-year-old patient had five episodes of rhabdomyolysis triggered by infections. Tandem mass spectrometry was normal. A 16-year-old female patient was hospitalized eight times due to recurrent rhabdomyolysis. Increased levels of C14:2, C14:1, and C14 were determined in tandem mass spectrometry. Final diagnoses were carnitine palmitoyltransferase II (CPT II) deficiency and very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency. Increased serum levels of long-chain acylcarnitine can guide to the diagnosis of lipid metabolism disorders. Serum ACP should be performed before enzyme assay and genetic studies.

Key Words

Carnitine palmitoyltransferase II deficiency, recurrent rhabdomyolysis, acylcarnitine profile, very long-chain acyl-CoA dehydrogenase deficiency

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Introduction

Metabolic myopathies due to disorders of lipid metabolism are a heterogeneous group of diseases that develop with a hereditary enzyme defect at any level of lipid metabolism. Lipid metabolism disorder-induced myopathy can be clinically silent in childhood and/or present only with elevated creatine kinase (CK) levels. Newborns may present with hypotonia, hypoglycemia, cardiomyopathy, arrhythmia, and convulsions, while progressive proximal muscle weakness or recurrent episodes of muscle weakness accompanied by rhabdomyolysis/myoglobinuria may be observed in older ages.[1]

Carnitine palmitoyltransferase II (CPT II) deficiency is an important metabolic cause of recurrent rhabdomyolysis in children and young adults and is usually triggered by strenuous exercise, prolonged fasting, cold, fever, or infections.[2] Myoglobinuria occurs in about 80% of cases.[3] Laboratory findings during the episodes include high CK levels and metabolic acidosis; plasma carnitine levels are low, but long-chain acylcarnitine levels are elevated. Diagnosis is confirmed by a deoxyribonucleic acid (DNA) or enzyme assay.[4]

Late onset form of very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency presents in the 2nd decade of life or later with recurrent rhabdomyolysis with conditions that require lipolysis. Diagnosis requires high clinical suspicion and can be performed by gas chromatographic analysis of plasma fatty acids, organic acid analysis of the urine, and VLCAD enzyme activity.[4]

Dried blood spot (DBS) acylcarnitine profile (ACP) analysis by tandem mass spectrometry still has high specificity and sensitivity for detecting clinically significant disease in the newborn period. However, there is little knowledge on detection rates of disorders of lipid metabolism by serum or DBS ACP outside the neonatal period, particularly with respect to different variants first presenting in adolescent or adulthood.

Acylcarnitine analysis is now widely available as a noninvasive initial investigation in patients suspected to have underlying

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disorders of lipid metabolism.[5,6] DBS and/or plasma/serum ACPs have been used according to the preferences of different investigators.

Recurrent rhabdomyolysis due to lipid metabolism disorders have been rarely diagnosed in childhood and in adolescence. We report two cases of recurrent rhabdomyolysis due to VLCAD and CPT II deficiency and we also report the clinical and laboratory differences between VLCAD and CPT II deficiency.

Case Reports

Case 1

A 13-year-old female patient presented to the hospital with complaints of myalgia, weakness, and dark urine. Her medical history revealed that she had muscle weakness and muscle cramps at the end of long-distance walking from early childhood. She had five episodes of rhabdomyolysis triggered by infections so far. Her two brothers also had a history of episodes of rhabdomyolysis. On physical examination, her upper and lower extremity muscle strength was 3-4/5, and deep tendon reflexes were normoactive. Serum CK, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, and serum myoglobin were 107,290 U/L, 888 U/L, 695 U/L, 57 mg/dL, 7.02 mg/dL, and > 1,200 μg/L, respectively. She had dark urine with no hemoglobin and erythrocytes. Tandem mass spectrometry was normal. The patient was immediately given fluid supply combined with bicarbonate infusions. Hemodialysis was commenced because of hypertension with a progressive increase in creatinine levels. The symptoms were controlled with appropriate medical treatment and hemodialysis. The recurrent attacks and family history suggested an inherited cause of rhabdomyolysis. Serum creatinine kinase value was completely normal between the attacks. Genetic analysis of the CPT II gene revealed homozygosity for the SI13L mutation. This attack was treated with intense hydration and bicarbonate treatment and she did not develop any complications. Frequent meals with carbohydrate-rich intake before exercise and restriction of long-chain fatty acid intake along with medium-chain fatty acid supplementation were recommended in order to prevent further attacks. Clinical and laboratory characteristics are shown in Table 1.

Case 2

A 16 year-old previously healthy girl presented with leg pain and weakness. Six months previously, she experienced generalized muscle pain after basketball training and diagnosed with rhabdomyolysis and acute renal failure. She recovered with hemodialysis. Since then, due to episodes of rhabdomyolysis occurring after exercise, she was hospitalized eight times. On physical examination, the upper and lower extremity muscle strength was 4/5 and deep tendon reflexes were hypoactive. Initial laboratory results were as follows: Serum CK 42,670 U/L, aspartate aminotransferase 538 U/L, alanine aminotransferase 276 U/L, blood urea nitrogen 51 mg/dL, creatinine 2.4 mg/dL, and serum myoglobin > 1,200 μg/L.

This episode of rhabdomyolysis recovered completely with intense hydration and bicarbonate infusion. Tandem test performed during an episode of rhabdomyolysis revealed increased levels of C14:2, C14:1, and C14. We considered VLCAD deficiency due to the increased level of C14:1. Very long-chain fatty acid acyl CoA dehydrogenase activity was low (4.3 nmol/min/mg protein; N: 5.1-21.7) in skin-derived fibroblast cultures. Due to frequently recurrent episodes of rhabdomyolysis, enteral nutrition products containing medium-chain fatty acids were started. Dietary regulation provided significant decrease in the number and severity of episodes of rhabdomyolysis. After diet treatment, the patient did not have a further attack of rhabdomyolysis requiring hospitalization during the 6 months follow-up. Clinical and laboratory characteristics are shown in Table 1.

Discussion

CPT II deficiency is the most common disorder of lipid metabolism causing recurrent myoglobinuria and rhabdomyolysis. Clinically, almost all individuals with the myopathic form experience myalgia. Occasionally, muscle cramps occur, although they are not typical of the disease.[3,4]

Table 1: Evaluation of clinical and laboratory characteristics of cases

Clinical and laboratory findings	Case 1 CPT II deficiency	Case 2 VLCAD deficiency
The first episode of rhabdomyolysis (age)	6	16
Trigger factors	Infections	Exercises
History of consanguinity	Yes	No
Hemodialysis	Yes	Yes
Electromyography	Normal	Mild myopathy in proximal muscle
Muscle biopsy	Normal	Normal
Tandem mass spectrometry (during an attack)	Normal	C14:2=0.56 (N <0.41) C14:1=1.39 (N <0.33) C14=0.48 (N <0.36)
Ecocardiography	Normal	Normal
Treatment	Carbohydrate-rich and long-chain fat restricted diet	Medium-chain fatty acid containing formula
CPT II mutation	SI13L homozygous mutation	Negative
VLCAD enzyme activity (fibroblast culture)	–	4.3 nmol/min/mg protein N: 5.1-21.7

CPT II = Carnitine palmitoyltransferase II deficiency, VLCAD = Very long-chain acyl-CoA dehydrogenase, N = Normal

Myoglobinuria is recognized as an important clinical marker in CPT II deficiency.[4] However, myoglobinuria was not determined in the medical history of 14 and 21% of the patients diagnosed with CPT II in two different studies, respectively.[3,7] Our case did not have myoglobinuria, but her two brothers had a history of rhabdomyolysis and myoglobinuria, therefore, we considered primarily CPT II deficiency. We identified SI13L homozygous mutation in CPTII gene analysis. Tandem analysis in CPT II deficiency reveals elevation of C12 to C18 acylcarnitines, notably of C16 and C18:1. However, DBS ACP of our case was normal.[8] CPT II deficiency should be considered in patients with recurrent episodes of rhabdomyolysis triggered by exercise, fasting, and infection. DNA and enzyme assay should be performed to confirm the diagnosis. Normal DBS ACP does not exclude CPT II deficiency. Serum ACP should be performed before enzyme assay. In our patient, serum ACP could not be obtained due to a lack of technical requirements in our laboratory.

Al-Thihli *et al*., reported that adult cases with CPT II have more stunning abnormality in serum versus DBS. In this study, long-chain acylcarnitines were more markedly elevated in serum samples from confirmed CPT II cases as compared to matched DBS profiles. According to their evaluation, the sensitivity of the serum ACP was 100% compared to a sensitivity of 71% for DBS ACP. Al-Thihli *et al*., determined that this finding provides initial evidence that serum ACP can be more sensitive than DBS ACP in detecting disorders of lipid metabolism.[9]

Late-onset episodic myopathic VLCAD deficiency presents with intermittent rhabdomyolysis, muscle cramps and/or pain, and/or exercise intolerance.[4] Rhabdomyolysis attacks often occur late in adolescents and adults. Increased C14:1 carnitine levels were reported to be the most important laboratory findings.[10] The key metabolites that are most often abnormal in VLCAD deficiency are C14:1, C14:2, C14, and C12:1.[11] Postprandial acylcarnitine levels measured by tandem mass spectrometry are important for diagnosis and should be performed in patients with unexplained episodes of exercise intolerance and rhabdomyolysis. In our case, despite the absence of any complaint in the past, exercise intolerance was described for the last 6 months, and the onset of the first episode of rhabdomyolysis was 16 years of age. In our case, all the attacks were triggered by exercise and often after low-intensity prolonged exercise. In our case, tandem mass examination during an acute episode of rhabdomyolysis showed an increase in the level of C14, C14:1, and C14:2 carnitine (DBS). Due to the increased level of C14:1, VLCAD deficiency was primarily considered. In our case, very long-chain fatty acid acyl CoA dehydrogenase enzyme activity was under normal ranges (4.3 nmol/min/mg protein; N: 5.1-21.7) in skin-derived fibroblasts cultures.

Acylcarnitine profiling in DBSs continues to be an important testing approach in clinical diagnostic settings in view of ease of collection, shipping, and storage. The quantity of blood present in the paper varies by hematocrit, diameter of blood spot, degree of saturation, and degree of hemolysis.[12] Uncertainty of the true blood volume along with variable extraction efficiency contributes to imprecision.[13] Therefore, only dry blood spot ACP should not be used for the diagnosis, results should be verified with serum ACP.

Early detection and treatment lead a significant reduction in morbidity and mortality. Pre-exercise carbohydrate-rich diets, restriction of long-chain fat intake along with medium-chain fatty acid supplementation are recommended.[4,14] In our case diagnosed with CPT II deficiency, the frequency and severity of episodes of rhabdomyolysis decreased by avoiding infection and with dietary recommendations, whereas, in our second case diagnosed with VLCAD deficiency, the frequency and severity of episodes of rhabdomyolysis decreased with enteral nutrition products containing medium-chain fatty acids.[4,14]

Disorders of lipid metabolism should be considered in the differential diagnosis of patients with recurrent episodes of rhabdomyolysis triggered by exercise, fasting, and infection. Increased serum levels of long-chain acylcarnitine can guide to the differential diagnosis of VLCAD and CPT II deficiencies. Given the treatable nature of disorder of lipid metabolism and the morbidity and mortality associated with rhabdomyolysis, DBS ACP and/or serum ACP testing is justifiably advised in children and adolescent presenting with recurrent rhabdomyolysis.

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