Carnitine Palmitoyl Transferase II Deficiency in an Adolescent Presenting With Rhabdomyolysis and Acute Renal Failure

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Abstract: The most common cause of recurrent rhabdomyolysis in childhood is inherited metabolic disorders. Carnitine palmitoyl transferase II (CPT II) deficiency is a lipidosis and is a common cause of inherited recurrent myoglobinuria. The disease is inherited in autosomal recessive trait, and the clinical phenotype ranges from a severe and multisystemic infantile form to a milder muscle form, which is characterized with rhabdomyolysis and myoglobinuria. Exercise, infection, fasting, and cold are the most important triggering factors of rhabdomyolysis in CPT II deficiency. The severity of attacks is highly variable and some of these attacks may be complicated by acute renal failure. We report a case of a 13-year-old girl with recurrent rhabdomyolysis due to CPT II deficiency whose last attack was complicated by acute renal failure.

Key Words: carnitine palmitoyl transferase II deficiency, rhabdomyolysis, acute renal failure, adolescent

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Rhabdomyolysis is a common clinical syndrome, which can result from a wide variety of conditions such as trauma, exercise, medications, infection, and inherited metabolic disorders. Most of the patients present with the triad of myalgia, weakness, and dark urine.[1] The diagnosis is supported by elevated creatinine kinase levels and confirmed by the measurement of myoglobin levels in the urine and serum. The most frightening complication is acute renal failure, which may develop in 7% of cases.[2,3] Inherited metabolic disorders are the most common cause of recurrent rhabdomyolysis in children and adults.[1] We report a case of a 13-year-old girl with recurrent rhabdomyolysis due to carnitine palmitoyl transferase II (CPT II) deficiency whose last attack was complicated by acute renal failure.

CASE

The patient was admitted to an emergency department with a 3-day history of myalgia, generalized muscular weakness, and extremely dark coloring of urine. The patient had experienced difficulty and cramps with long-distance walking in early childhood. She had 5 attacks of rhabdomyolysis, which were triggered by infections previously. These attacks were treated with intense hydration and bicarbonate treatment and she did not develop any complications. The parents were consanguineous and her 2 brothers also had histories of recurrent rhabdomyolysis. At presentation, muscle strengths in proximal and distal muscles of upper and lower extremities were 3 to 4/5. Deep tendon reflexes were normoactive and there was no lateralizing neurologic deficit. The remainder of the physical examination was normal. Serum creatine kinase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, and serum myoglobin levels were 107,290 U/L (range, 55–170 U/L), 888 U/L (5–34 U/L), 695 U/L (0–55 U/L), 57 mg/dL (5.1–16.8 mg/dL), 7.02 mg/dL (0.2–0.4 mg/dL), and greater than 1200 ng/mL (6–85 ng/mL), respectively (Fig. 1). She had dark urine with no hemoglobin and erythrocytes. The patient was immediately given intravenous fluid supply combined with intravenous bicarbonate infusions. Hemodialysis was commenced because of hypertension with a progressive increase in creatinine levels. The signs and 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. Electromyography and muscle biopsy revealed no abnormality. The genetic analysis of the *CPT II* gene revealed homozygosity for the *SI13L* mutation. 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 to prevent further attacks.

DISCUSSION

The most common cause of recurrent rhabdomyolysis in childhood is inherited metabolic disorders. Among the inherited metabolic causes, disorders of lipid metabolism (lipidoses), disorders of glycogen metabolism (glycogenoses), and myoadenylate deficiency are the most common.[1] Carnitine palmitoyl transferase II deficiency is a lipidosis and is a common cause of inherited recurrent myoglobinuria. Carnitine palmitoyl transferase II is localized in the inner mitochondrial membrane and catalyzes the formation of acyl-coenzyme A from acylcarnitine and acyl-coenzyme A.[1,4] The disease is inherited as an autosomal recessive trait. The clinical phenotype ranges from a severe and multisystemic infantile form to a milder muscle form, which is characterized with rhabdomyolysis and myoglobinuria. In contrast to glycogenoses, the patients are symptom-free between the attacks. Myalgia starts in childhood, whereas attacks with myoglobinuria mostly emerge in late childhood and adolescence. Exercise, infection, fasting, and cold are the most important triggering factors of rhabdomyolysis in CPT II deficiency.[5] The severity of attacks is highly variable and some of these attacks may be complicated by acute renal failure.[4] Our patient experienced difficulty and cramps in long-distance walking in early childhood. Rhabdomyolysis attacks started at the age of 6 years, all of which were triggered by infections. Only the last attack was complicated by acute renal failure.

The differential diagnosis of recurrent rhabdomyolysis usually requires a good history intake and a clinical suspicion. Patients with McArdle disease usually have exercise intolerance,

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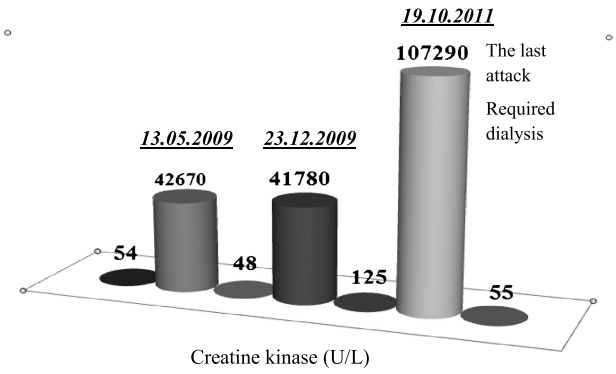

FIGURE 1. Creatine kinase values (between attacks and during attacks).

myalgias, in addition to rhabdomyolysis.[6] During the first few minutes of high-intensity activity, patients with McArdle disease develop fatigue, weakness, and muscle aches, but a brief rest can improve exercise tolerance (second wind phenomenon).[1,6] The clinical presentation of Tarui disease can be very similar to McArdle disease (out-of-wind phenomenon), but carbohydrate intake usually exacerbates exercise intolerance.[1,7] In contrast to patients with McArdle and Tauri disease, patients with CPT II deficiency have normal rise in lactic acid during muscle exercise. Patients with CPT II deficiency have not experienced second wind phenomenon. Rhabdomyolysis attacks of this disease are commonly provoked by prolonged low-intensity exercise, cold, fasting, and infection.[7] Our patient has not experienced second wind phenomenon and attacks provoked by infections. If exercise-induced rhabdomyolysis or metabolic myopathy is suspected, further studies may be required, including forearm exercise test, muscle biopsy, and genetic testing.[1,7] The diagnostic workup of tests regarding recurrent rhabdomyolysis frequently includes a muscle biopsy. In contrast to carnitine deficiency, which shows lipid accumulation, muscle biopsies in CPT II deficiency are normal or may show nonspecific myopathic changes.[4,8] The electromyography and muscle biopsy of our patient were normal. Molecular genetic and biochemical analyses are the hallmark in diagnosis. In CPT II deficiency, *S113L* mutation is the most common, followed by *P50H* and *Q413fs* and *F448L* mutations. More than 95% of the patients carry the *S113L* mutation at least in 1 allele. Carnitine palmitoyl transferase II deficiency is not likely to be the diagnosis in patients who do not carry the *S113L* mutation and even less likely if the *P50H* and *Q413fs* and *F448L* mutations are also excluded.[4,9–11] The molecular testing of these 4 mutations can establish the diagnosis in three quarters of the patients by identifying mutations in both alleles. Carnitine palmitoyl transferase II deficiency may also be tested in muscle homogenates biochemically.[4] Our patient was homozygous for *S113L* mutation. There is a genotype-phenotype correlation in CPT II deficiency. Mild missense mutations such as *S113L* mutation are associated with the muscle form of the disease, whereas truncating mutations such as *Q413fs* and *F448L* mutations are related to multisystemic infantile or lethal form.[12–14] Compound heterozygosity for a mild and severe mutation may present as a mild muscle or severe lethal form.[4,13] Our patient had a mild muscle form of the disease as expected in homozygous *S113L* mutation. There is no definitive treatment of CPT II deficiency, and carbohydrate-rich intake before exercise and restriction of long-chain fatty acid intake along with medium-chain fatty acid supplementation are recommended. Intense hydration is very important to prevent renal complications.[4,15] In conclusion, CPT II deficiency should be suspected in children with recurrent rhabdomyolysis requiring hemodialysis. Molecular genetic analysis of the related gene should be performed to elucidate the cause of the disease and families must have precise genetic counseling.

REFERENCES

1. Elsayed EF, Reilly RF. Rhabdomyolysis: a review, with emphasis on the pediatric population. *Pediatr Nephrol*. 2010;25:7–18. Review.
2. Sauret JM, Marinides G, Wang GK. Rhabdomyolysis. *Am Fam Physician*. 2002;65:907–912.
3. Zager RA. Studies of mechanisms and protective maneuvers in myoglobinuric acute renal injury. *Lab Invest*. 1989;60:619–629.
4. Deschauer M, Wieser T, Zierz S. Muscle carnitine palmitoyltransferase II deficiency: clinical and molecular genetic features and diagnostic aspects. *Arch Neurol*. 2005;62:37–41.
5. Kilfoyle D, Hutchinson D, Potter H, et al. Recurrent myoglobinuria due to carnitine palmitoyltransferase II deficiency: clinical, biochemical, and genetic features of adult-onset cases. *N Z Med J*. 2005;118:U1320.
6. Burr ML, Roos JC, Ostör AJ. Metabolic myopathies: a guide and update for clinicians. *Curr Opin Rheumatol*. 2008;20:639–647.
7. Berardo A, DiMauro S, Hirano M. A diagnostic algorithm for metabolic myopathies. *Curr Neurol Neurosci Rep*. 2010;10:118–126.
8. Engel AG, Rebouche CJ. Carnitine metabolism and inborn errors. *J Inherit Metab Dis*. 1984;7:38–43.
9. Deschauer M, Wieser T, Schröder R, et al. A novel nonsense mutation (515del4) in muscle carnitine palmitoyltransferase II deficiency. *Mol Genet Metab*. 2002;75:181–185.
10. Deschauer M, Chrzanowska-Lightowlers ZM, Biekmann E, et al. A splice junction mutation in muscle carnitine palmitoyltransferase II deficiency. *Mol Genet Metab*. 2003;79:124–128.
11. Wieser T, Deschauer M, Olek K, et al. Carnitine palmitoyltransferase II deficiency: molecular and biochemical analysis of 32 patients. *Neurology*. 2003;60:1351–1353.
12. Elpeleg ON, Hammerman C, Saada A, et al. Antenatal presentation of carnitine palmitoyltransferase II deficiency. *Am J Med Genet*. 2001;102:183–187.
13. Vladutiu GD, Quackenbush EJ, Hainline BE, et al. Lethal neonatal and severe late infantile forms of carnitine palmitoyltransferase II deficiency associated with compound heterozygosity for different protein truncation mutations. *J Pediatr*. 2002;141:734–736.
14. Smeets RJ, Smeitink JA, Semmekrot BA, et al. A novel splice site mutation in neonatal carnitine palmitoyl transferase II deficiency. *J Hum Genet*. 2003;48:8–13.
15. Ørngreen MC, Ejstrup R, Vissing J. Effect of diet on exercise tolerance in carnitine palmitoyltransferase II deficiency. *Neurology*. 2003;61:559–561.