Therapeutic Options in Other Metabolic Myopathies

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Summary: Adult patients with metabolic myopathies typically present with exercise-induced pain, cramps, fatigue, and myoglobinuria. The current therapeutic options of glycogen and lipid storage myopathies include dietary treatments, exercise training, and pharmacological supplementations. Herein is a review of evidence from randomized controlled trials in McArdle disease (glycogen storage disease type V, muscle phosphorylase deficiency)

and carnitine palmitoyltransferase (CPT) 2 deficiency. A brief overview on current treatment options in rhabdomyolysis is also included because patients with McArdle disease and CPT 2 often experience such potentially life-threatening complications. **Key Words:** McArdle disease, rhabdomyolysis, metabolic myopathy, carnitine palmitoyltransferase (CPT) 2 deficiency, glycogen storage disease, lipid storage disease.

INTRODUCTION

Glycogen and lipid storage myopathies are rare hereditary disorders that either affect the breakdown of glycogen to glucose-1-phosphate or degradation of glucose through the glycolytic enzyme cascade, or affect the mitochondrial fatty acid oxidation. Among these metabolic myopathies, McArdle disease and carnitine palmitoyltransferase (CPT) 2 deficiency are the most frequent disorders in adult patients.

McArdle disease is caused by the absence of the glycogenolytic enzyme, muscle phosphorylase.¹ The inheritance is autosomal recessive, and the most common mutation in Northern Europe and North America is the nonsense mutation R50X present in approximately 50% of mutant alleles. The preferred method of diagnosis is by muscle histochemistry and measuring phosphorylase enzyme activity in muscle. The main complaints are exercise-induced muscle pain in working muscles (contractures) and premature fatigue, both of which often start in childhood. Frequently, patients report a second-wind phenomenon, which is a sudden, spontaneous improvement in exercise capacity after seven to eight minutes of exercise, and is caused by an enhanced uptake and oxidation of glucose and fatty acids. Rhabdomyolysis can occur with sustained exercise. Most patients develop adaptive behaviors and are able to live normal

lives. However, a small proportion of patients develop a severe phenotype with fixed muscle weakness and limitation in daily-life activities with advancing age. The underlying reasons are inability to mobilize muscle glycogen stores during anaerobic exercise and impaired oxidative phosphorylation because of low substrate flux through the tricarboxylic cycle.²

The CPT system is made up of two separate proteins located in the outer (CPT 1) and inner (CPT 2) mitochondrial membranes, which import long-chain fatty acids from the cytosol into the mitochondrial matrix.³ CPT 2 deficiency is also an autosomal recessive disease with two clinical presentations. The more prevalent myopathic form of CPT 2 deficiency is characterized by episodes of rhabdomyolysis under particular conditions that increase the requirement for fatty acid oxidation, such as low-carbohydrate and high-fat diet, fasting, exposure to excessive cold, lack of sleep, and prolonged exercise. Diagnosis requires biochemical investigations and genetic analysis. Although more than 40 mutations in the CPT 2 gene are known, there is a prevalent missense mutation S113L in patients with muscle CPT 2 deficiency that is found in about 60% of mutant alleles. The rare multisystemic infantile form of CPT 2 deficiency presents as severe attacks of hypoketotic hypoglycemia, associated with cardiomyopathy and hepatomegaly.

In this article I will emphasize treatment options in McArdle disease and CPT 2 deficiency that are based on controlled, prospective, therapeutic trials. Because both conditions may cause rhabdomyolysis, I will also pro-

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vide some recommendations for treating this potentially life-threatening complication.

THERAPEUTIC OPTIONS IN MCARDLE DISEASE

Creatine treatment

Creatine treatment has beneficial effects in some hereditary myopathies. Six controlled, randomized studies have recently appeared that show improvement in maximum voluntary contraction in patients with dystrophinopathies or myotonic dystrophies. Overall, a Cochrane meta-analysis favors creatine in these patients.⁴ Creatine is an amino acid formed from arginine and glycine in a two-step reaction in the kidneys and liver. After this, it traverses to the skeletal muscle where it is transported across the cell membrane via a sodium-dependent creatine membrane transporter.⁵ Due to the equilibrium reaction of creatine kinase, one has to expect that an uptake of creatine by the muscle fibers results in an elevation of intracellular phosphocreatine (PCr) levels. Transphosphorylation of adenosine triphosphate (ATP) on creatine and subsequent rephosphorylation of adenosine diphosphate by oxidative phosphorylation should result in elevated PCr/ATP ratios visible in phosphorus 31 magnetic resonance spectroscopy (MRS) of muscle. However, in patients with McArdle disease, oral creatine supplementation in both high (150 mg/kg daily) and low (60 mg/kg daily) doses did not result in elevated PCr/ATP levels.^{6,7} With low-dose creatine, working capacity for ischemic exercise improved, and we found a higher consumption of PCr during aerobic and ischemic low-level exercise in patients with McArdle disease. However, high-dose creatine cannot be recommended because it worsened clinical symptoms of exercise intolerance; patients reported an increase in both the number of pain episodes and the myalgia pain score.

Diet

In a crossover, open-design study, carbohydrate-rich (20% fat, 15% protein, 65% carbohydrate) *versus* protein-rich (15% fat, 55% proteins, 30% carbohydrate) diets were compared in patients with McArdle disease.⁸ After each diet, exercise tolerance and maximal work capacity were tested on a cycle ergometer by using a constant workload for 15 minutes followed by an incremental workload to exhaustion. The carbohydrate-rich diet improved the maximal work capacity and the exercise tolerance of submaximal workloads.

Moderate aerobic exercise

Moderate aerobic exercise was tested in patients with McArdle disease who pedaled a cycle ergometer for 30 to 40 minutes per day, four days a week, for 14 weeks, at an intensity corresponding to 60% to 70% of maximal heart rate.⁹ This exercise program increased average

work capacity, oxygen uptake, cardiac output, and mitochondrial enzyme levels without causing pain or cramping or increasing serum creatine kinase (CK). This study suggests that regular, submaximal aerobic exercise increases oxidative capacity and should be a consistent component of therapy in patients with McArdle disease.

Ramipiril

In patients with McArdle disease, a genotype (D/D) associated with higher angiotensin-converting enzyme (ACE) activity showed a more severe phenotype of exercise intolerance.^{10,11} It was suggested that modulation of ACE activity through the use of inhibitors like ramipril may positively affect disease expression and limitations of exercise capacity. A controlled trial of 12 weeks of low-dose ramipril treatment (2.5 mg daily) in patients with McArdle disease did not show changes in primary outcome measures of exercise physiology, although it did show a possible benefit in patients with the D/D ACE genotype.¹²

Aminoglycosides

Aminoglycosides may allow the potential to read through stop codons and thus may induce synthesis of a full-length protein. In most patients with McArdle disease, the primary genetic abnormality is a missense mutation R50X in the phosphorylase gene leading to a premature stop codon. In an open study, four R50X homozygous McArdle patients were given daily i.v. gentamicin sulphate at 8 mg/kg/day for 10 days.¹³ This short-term aminoglycoside treatment appeared to have no effect on muscle energy metabolism assessed by ³¹P-MRS. This might have been because the treatment was not given for long enough, or because the type of nonsense mutation was not amenable to the effects of the drug. This potential therapeutic strategy may be exploited with new pharmacological compounds in the future.

Sucrose

Sucrose is a disaccharide of glucose and fructose. It is the most important sugar in plants. Six patients with McArdle disease were tested after ingestion of either 75 g of sucrose 40 minutes before exercise or 37 g of sucrose 5 minutes before exercise.¹⁴ Treatment effects were assessed by monitoring heart rate and perceived exertion during exercise. Both sucrose treatments improved exercise tolerance, and the low-dose sucrose given 5 minutes before exercise had a more sustained effect on exercise capacity than the higher dose given 40 minutes before exercise. The authors recommend low-dose sucrose ingestion immediately before episodes of more strenuous exercise. This provides a sustained elevation in plasma glucose during exercise, which partially rescues muscle oxidative metabolism early in exercise.

THERAPEUTIC OPTIONS IN CPT 2 DEFICIENCY

In general, patients with CPT 2 deficiency must avoid triggering factors of metabolic crisis like fasting, cold, or prolonged exercise.

Glucose

Glucose infusion had beneficial effects in CPT 2 patients, indicated by longer exercise duration, lower level of perceived exertion, and lower heart rate during infusion. However, oral glucose did not achieve the same effects because of lower glucose availability and higher insulin levels, which inhibit muscle glycogenolysis.¹⁵ Therefore, oral glucose before exercise is of no practical value for patients with CPT 2 deficiency. In a subsequent controlled trial, the same group showed that high-carbohydrate diet (20% fat, 15% protein, 65% carbohydrate) improves exercise tolerance in CPT 2-deficient patients as indicated by lowering of perceived exertion and increased duration of exercise.¹⁶

Fibrates

Fibrates raise high-density lipoprotein (HDL) cholesterol by upregulating mRNA levels of genes involved in lipid metabolism through activating peroxisome proliferator activated receptors (PPARs). Bezafibrate treatment of mild-type CPT 2-deficient fibroblasts resulted in a time- and dose-dependent increase in CPT 2 mRNA and residual enzyme activity, and led to normalization of 3H-palmitate and 3H-myristate cellular oxidation rates. Bezafibrate did not correct fatty acid oxidation in fibroblasts from CPT 2 patients with severe phenotype.¹⁷ A second study of the same group showed that bezafibrate and specific agonists of PPAR stimulated fatty acid oxidation and increased CPT 2 activity in CPT 2-deficient myoblasts.¹⁸ These studies suggest that PPARs could be therapeutic targets for correction of hereditary β -oxidation defects. This has led to an open therapeutic trial in France with bezafibrate (begun in 2006) in patients with muscle CPT 2 deficiency that will clarify whether this substance could provide a new treatment strategy (<http://clinicaltrials.gov/ct2/show/NCT00336167>).

Anaplerotic diet

Anaplerotic diet using medium-odd-chain triglycerids (triheptanoin) improved cardiomyopathy, muscle weakness, and rhabdomyolysis in an open study in three patients with very-long-chain acyl-coenzyme A dehydrogenase deficiency.¹⁹ This kind of therapy is based on the concept that triheptanoin as an anaplerotic compound provides an alternative substrate for both the tricarboxylic cycle and electron transport chain and thus may restore energy production.²⁰ Whether such an anaplerotic therapy also improves symptoms of exercise intolerance in patients with CPT 2 deficiency needs to be investigated in controlled trials.

TREATMENT OF RHABDOMYOLYSIS

Rhabdomyolysis is characterized by acute damage of the sarcolemma of the skeletal muscle leading to the release of potentially toxic muscle cell components, most notably CK and myoglobin, into the circulation. Typical symptoms include muscle pain, weakness, and dark urine. This disorder may result in potentially life-threatening complications, such as acute myoglobinuric renal failure (which occurs in 4%-33% of patients), cardiac dysrhythmias via electrolyte abnormalities, disseminated intravascular coagulation, and compartment syndrome. The condition is etiologically heterogeneous and may result from metabolic myopathies and multiple other causes affecting muscle membranes, membrane ion channels, and muscle energy supply (e.g., exertion, crush injury and trauma, alcoholism, drugs, and toxins). The mainstay of treatment is hospitalization with early aggressive i.v. fluid replacement to minimize the occurrence of renal failure and correction/prevention of electrolyte abnormalities. Additional adjunctive therapies, such as alkalinization of the urine with sodium bicarbonate, diuretic therapy, and renal protection with mannitol, although commonly recommended, are of unproven benefit.²¹ In severe cases, appropriate management may also include continuous venovenous hemofiltration, mechanical ventilatory support, and administration of antibiotics. The overall prognosis for rhabdomyolysis is favorable when treated with early and aggressive fluid resuscitation, and full recovery of renal function is common. Irrespective of the cause of rhabdomyolysis, the mortality rate may still be as high as 8%.²¹

CONCLUSIONS

Thus far, no causative therapy in lipid and glycogen storage myopathies (except for the lysosomal Pompe disease) is available. Patients with McArdle disease and CPT 2 deficiency must be advised to avoid trigger factors of rhabdomyolysis and should follow a high-carbohydrate diet. Nutritional supplementation with low-dose creatine or sucrose may help to reduce symptoms of exercise intolerance in McArdle disease. There is an urgent need to develop molecular-oriented therapeutic strategies in the future.

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