Carnitine palmitoyltransferase II deficiency: Successful anaplerotic diet therapy
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ABSTRACT

Background: Carnitine palmitoyltransferase II (CPT II) deficiency is an important cause of recurrent rhabdomyolysis in children and adults. Current treatment includes dietary fat restriction, with increased carbohydrate intake and exercise restriction to avoid muscle pain and rhabdomyolysis.

Methods: CPT II enzyme assay, DNA mutation analysis, quantitative analysis of acylcarnitines in blood and cultured fibroblasts, urinary organic acids, the standardized 36-item Short-Form Health Status survey (SF-36) version 2, and bioelectric impedance for body fat composition. Diet treatment with triheptanoin at 30% to 35% of total daily caloric intake was used for all patients.

Results: Seven patients with CPT II deficiency were studied from 7 to 61 months on the triheptanoin (anaplerotic) diet. Five had previous episodes of rhabdomyolysis requiring hospitalizations and muscle pain on exertion prior to the diet (two younger patients had not had rhabdomyolysis). While on the diet, only two patients experienced mild muscle pain with exercise. During short periods of noncompliance, two patients experienced rhabdomyolysis with exercise. None experienced rhabdomyolysis or hospitalizations while on the diet. All patients returned to normal physical activities including strenuous sports. Exercise restriction was eliminated. Previously abnormal SF-36 physical composite scores returned to normal levels that persisted for the duration of the therapy in all five symptomatic patients.

Conclusions: The triheptanoin diet seems to be an effective therapy for adult-onset carnitine palmitoyltransferase II deficiency. Neurology 2008;71:260–264

GLOSSARY

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATP = adenosine triphosphate; BHP = β-hydroxybutyrate; BKP-CoA = β-ketopentanoyl–coenzyme A; CPK = creatine phosphokinase; CPT II = carnitine palmitoyltransferase II; LDL = low-density lipoprotein; MCT = medium-chain triglyceride; PCS = physical composite score; SF-36 = 36-item Short-Form Health Status survey.

Carnitine palmitoyltransferase II (CPT II) deficiency is an autosomal recessive disorder that can present with three clinical phenotypes: neonatal (lethal), childhood, and adult onset. These patients have recurrent hospitalizations for rhabdomyolysis usually beginning in the second decade that can lead to renal failure. The current treatment involves dietary restriction of fat with increased carbohydrate intake. This regimen has resulted in short-term increased exercise tolerance but has not prevented recurrent rhabdomyolysis or restored patients to a normal lifestyle. Exercise restriction is recommended for all patients to avoid episodes of muscle pain and rhabdomyolysis. An alternate diet strategy involves substitution of medium-chain triglyceride (MCT) oil for long-chain fat with increased carbohydrate intake. MCT oil contains octanoate (C₈) and decanoic (C₁₀) acids bound to glycerol. Because they can enter the mitochondrion as carboxylates, oxidation of these fatty acids is generally independent of CPT I, CPT II, and the carnitine–acylcarnitine translocase. This dietary approach has also not been effective in controlling muscle pain, preventing hospitalizations due to rhabdomyolysis, or...
Restoring muscle strength and endurance. After the attenuation of rhabdomyolysis in other long-chain fat oxidation disorders with a diet containing triheptanoin (glyceryl triheptanoate), we now report the experience with seven patients with childhood- and adult-onset CPT II deficiency who received triheptanoin for up to 61 months.

METHODS Diagnostic methods. CPT II enzyme assays, in vitro palmitate oxidation, DNA analysis, acylcarnitine analysis, plasma fatty acid metabolites (ketone bodies), and protein measurements were performed for diagnostic and monitoring purposes. The 36-item Short-Form Health Status survey (SF-36) version 2.11 bioelectric impedance measurements, and serial blood and urine chemical measurements were obtained on each patient (for more detail, see e-Methods on the Neurology Web site at www.neurology.org).

Patient descriptions. Seven patients with CPT II deficiency, ranging in age from 10 to 55 years, were included in this study. Three of them (patients 3, 4, and 5) were siblings. Others included a 55-year-old woman (patient 1), a 54-year-old man (patient 2), a 30-year-old man (patient 6), and a 14-year-old boy (patient 7). Brief clinical summaries and results of enzyme assays and DNA analysis are available as supplemental material (see e-Patients).

Clinical protocol. This study required proof of CPT II deficiency by mutation analysis or enzyme assays from biopsies of muscle, fibroblasts, or fresh lymphocytes before patients could be included. All patients signed informed consent under Baylor University Medical Center’s Institutional Review Board 099-135 protocol registered under US Food and Drug Administration Investigational New Drug no. 59,303.

Initially, patients were evaluated for 5 days when baseline clinical and laboratory data were obtained. The triheptanoin diet was started by the second day with dose adjustments as required and daily educational sessions regarding management of the disorder. Patients were then followed up by repeat clinical and laboratory evaluations at approximately 2, 6, 12, and 18 months. After 18 months, they were given the choice of returning to conventional therapy or continuing the triheptanoin diet indefinitely. These patients elected to extend their participation, currently ranging from 40 to 61 months, providing additional safety and efficacy information about the triheptanoin diet.

Nutritional needs were based on recommended daily allowance guidelines for all patients. The average daily percent compositions of the diet during the protocol were as follows: protein 13.1%, carbohydrate 37.2%, and fat 20%. Triheptanoin (8.3 kcal/g) represented the balance of 30%. For adults and adolescents, the daily dose was 1 to 2 g/kg body weight. For children younger than 12 years, the daily dose of triheptanoin was usually 3 to 4 g/kg because of their greater daily caloric requirement. All patients consumed this daily amount of oil in four equal doses (three main meals and at bedtime). Triheptanoin was mixed in preferred foods, such as yogurt, pudding, or beverages. All patients were advised to limit consumption of simple sugars to prevent undue weight gain and optimize oxidation of triheptanoin. Further, they were advised to consume the oil slowly over a 20- to 30-minute period to avoid any gastric discomfort.

RESULTS Diagnostic testing. Obtaining the diagnosis can be extremely delayed (decades). Serum creatine phosphokinase (CPK) levels and blood acylcarnitine analyses were only abnormal during episodes of rhabdomyolysis. Only enzyme assay and in vitro fibroblast analysis were consistently reliable for diagnosis (see e-Patients and e-Methods).

Response to dietary triheptanoin. Triheptanoin was given in four equal doses (the three main meals and at bedtime) because of the rapid metabolism of triheptanoin (3–4 hours) when given enterally. Blood levels of propionylcarnitine increased from <1.0 μM to peak levels of approximately 4.0 μM at 90 to 120 minutes and decreased to approximately 2 μM by 180 minutes. Plasma ketone levels (β-hydroxybutyrate [BHP], β-ketopentanoate [BKP], β-hydroxybutyrate, and acetoadetate) followed a similar time course.

All patients tolerated the diet well without diarrhea or stomach cramps as long as they ingested their dose over a 20- to 30-minute period. None of them experienced sudden weight gain. Weight and height remained appropriate for age for all patients. Serial measurements of percent fat composition from baseline were available only for patients 1, 2, 3, and 6. The values for patient 1 increased from 25.9% to 31.2% over 30 months (reference range for age 21.1–26.1%). Patient 2 began at 17% and at 19 months was 20.8% (reference range 16.1–21.1%). Patient 3 had 18.0% fat at baseline increasing over 34 months to 21.5% (reference range 17.1–22.1%). At 6 months, patient 6 had decreased from 21.0% to 19.6% (reference range 13.1–18.1%). Because of lack of norms for children aged 10 years and younger (patients 4 and 5), baseline values were not measurable. At 18 and 28 months, the percent fat for patient 4, aged older than 11 years, decreased from 17.0% to 14.9% (reference range 17.1–22.1%). Patient 7 had only a normal baseline analysis.

Table 1 summarizes the hospitalizations for rhabdomyolysis and muscle pain on exertion before and after being on the triheptanoin diet. Except for patient 4, all had been hospitalized and had muscle pain on exertion sufficient to restrict exercise before starting the triheptanoin diet. Previous diet management was low fat, increased carbohydrate for all patients. Those younger than 14 years had an additional MCT oil supplement that ranged from 6% to 10% of daily caloric intake.

After the triheptanoin diet was initiated, most patients experienced some improvement in daily activities without discomfort by the end of the first week. Within 1 to 2 months, more impressive improvements in exercise tolerance had occurred. For those patients who adhered to the triheptanoin diet, none were hospitalized with rhabdomyolysis and only two...
experienced mild muscle pain with exercise. All seven patients were able to compete in team sports (volleyball, basketball, gymnastics, swimming, and tae kwon do). The older patients (nos. 1, 2, and 6) participated in swimming, aerobics, skiing, and hiking. These activities were not possible on their previous diet management. Consequently, exercise restriction was no longer necessary. In an attempt to prevent muscle pain, a dose of triheptanoin was recommended to be taken 30 minutes before strenuous physical activity.

However, two patients (nos. 3 and 7) stopped taking the oil for periods of 1 to 2 weeks. Both required hospitalization after strenuous exercise. Each returned to the triheptanoin diet with renewed exercise tolerance.

**SF-36 questionnaires.** These were administered at baseline and on subsequent visits. Table 2 shows the available sequential physical composite scores (PCS) for each patient at baseline and out to 33 months after starting the diet. PCS scores for the two relatively asymptomatic patients, nos. 4 and 5, were normal at baseline and remained normal after 28 months of treatment. Their older sibling, patient 3, had achieved a normal PCS score by 6 months that also remained normal. All three remained pain free after 45 months (patients 4 and 5) and 52 months (patient 3) on the diet. The other four patients showed significant enhancement of PCS scores from baseline ranging from $+1 \text{ SD}$ (patient 7) to as much as $+3 \text{ SDs}$ (patient 2) approaching or surpassing the normal score of 50 (table 2).

**Safety monitoring.** There seemed to be no evidence for toxicity from the triheptanoin diet. There were no consistent abnormalities in any of the serial laboratory results except for variations in CPK, associated with mild elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) when patients experienced mild discomfort.

Lipid profiles were generally unremarkable except in patients 1 and 2 (both older than 50 years), who had abnormal profiles at baseline and during the C7 diet. For patient 1, cholesterol was elevated intermittently, and triglycerides were initially elevated and later returned to normal. Low-density lipoprotein (LDL) cholesterol was normal at baseline but abnormal thereafter. Patient 2 was hypercholesterolemic throughout the diet protocol and LDL was persistently elevated. None of the other patients had any lipid abnormalities while taking triheptanoin.

Blood chemistries at baseline and during the triheptanoin diet were normal for glucose, potassium, carbon dioxide, anion gap, creatinine, and albumin. Blood urea nitrogen (BUN) was mildly elevated, intermittently, in patients 2, 3, and 5. Their levels were only 18 to 23 mg/dL, compared with the reference range of 7 to 17 mg/dL. Creatinine levels were never elevated in association with these minor BUN abnormalities. AST and

<table>
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<tr>
<th>Table 1</th>
<th>CPT II patients: Hospitalizations and muscle pain on exertion, before and after the triheptanoin diet</th>
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<tbody>
<tr>
<td>Patient</td>
<td>Duration on C7, mo</td>
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CPT II - carnitine palmitoyltransferase II.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Initial and subsequent SF-36 (PCS) scores</th>
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<tr>
<td>Patient</td>
<td>Baseline 19 mo 30 mo</td>
</tr>
<tr>
<td>1</td>
<td>Baseline 22 mo</td>
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<tr>
<td>2</td>
<td>Baseline 6 mo 18 mo 28 mo</td>
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<tr>
<td>3</td>
<td>Baseline 12 mo 18 mo 28 mo</td>
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<td>4*</td>
<td>Baseline 12 mo 18 mo 28 mo</td>
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<td>6</td>
<td>Baseline 6 mo</td>
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<tr>
<td>7</td>
<td>Baseline 4 mo</td>
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*Siblings of patient 3. SF-36 – 36-item Short-Form Health Status survey; PCS – physical composite score.
ALT levels were basically normal while on the diet. As expected, AST was mildly elevated only in association with increased CPK levels. There were a number of "subclinical" elevations of CPK (no perceived muscle discomfort). Only one patient (no. 5) had abnormal levels at each visit, ranging from 166 to 537 IU/L (reference range 30–135 IU/L). The total range of all CPK values for these patients while taking the diet was 35 to 869 IU/L.

None of the patients had any hematologic abnormalities during the study.

Blood palmitoylcarnitine levels were rarely abnormal, and levels of oleylcarnitine were only occasionally mildly increased but were not diagnostic for CPT II deficiency. Quantitative urinary organic acid excretion profiles did not show any persistent abnormalities (see table e-1 for more detail).

DISCUSSION Patients with the childhood- or adult-onset form of CPT II deficiency experience recurrent episodes of severe muscle pain associated with rhabdomyolysis accompanied with extreme elevation of serum CPK and myoglobinuria. These episodes are often triggered by fasting, infection, or excessive exercise. As reported in this and other studies, the diagnosis can be difficult to establish, often involving decades. Enzyme assay for CPT II activity from muscle biopsies, fibroblast cultures, and lymphocytes are uniformly definitive. Analysis for the "common" DNA mutation, S113L, was not always reliable, nor was acylcarnitine analysis or serum CPK, as seen in the results with our patients, except during episodes of rhabdomyolysis. Residual CPT II activity may be responsible for the difficulty in early recognition of this disorder.

Therapy has focused on reducing dietary fat intake while increasing carbohydrate mainly to reduce the abnormal accumulation of both long-chain acyl–coenzyme A (CoA) and acylcarnitine intermediates. During a rhabdomyolytic crisis, excessive lipolysis associated with myoglobinuria is the primary concern. Acute therapy includes glucose infusion (often with an insulin drip) to reduce lipid mobilization and large volumes of fluid and alkalinization to enhance renal excretion of myoglobin. The dietary restriction of fat, even with substitution of medium-chain even-carbon triglycerides (MCT oil), although a sound rationale, has not been successful, because exercise restriction is required, muscle pain on exertion persists, and recurrent hospitalizations continue to occur.

Skeletal muscle relies on oxidation of fat, glucose, and amino acids for energy. Our treatment hypothesis is based on the likelihood that energy metabolism is seriously compromised by the inability to fuel the citric acid cycle (CAC) by β-oxidation in this and other long-chain fat oxidation defects that feature recurrent rhabdomyolysis. For effective function of the CAC linked to the respiratory chain for adenosine triphosphate (ATP) production, adequate oxaloacetate along with acetyl-CoA is required for the citrate synthase reaction. Because glucose and medium-chain fatty acids (C₉ and C₁₀) can only provide acetyl-CoA, we evaluated the effect of triheptanoin as an intramitochondrial source of acetyl-CoA and also oxaloacetate derived from the propionyl-CoA moiety. When given enterally, 1 mole of triheptanoin provides 1 mole of glycerol and 3 moles of heptanoate. Heptanoate is almost totally taken up by the liver and does not require CPT I, carnitine–acyltransferase reaction in muscle. The result is increased ATP formation via the respiratory chain, potentially correcting the energy deficit.
Children and adults with CPT II deficiency are acutely aware of their physical limitations on a day-to-day basis, as evidenced by periods of muscle weakness, pain, and aching, related to mild to moderate exercise or illnesses.

Except for the two relatively asymptomatic children (patients 4 and 5), each patient in this study became aware of increased physical endurance without muscle fatigue or aching as early as the fourth day of therapy. Since beginning and adhering to the diet therapy, none of them required hospitalization for rhabdomyolytic episodes. All patients returned to unrestricted physical exercise. These activities included basketball, volleyball, skiing, aerobics, and near Olympic-type daily swimming protocols. Compared with their baseline evaluations, the PCS from the SF-36 questionnaire for these five symptomatic patients had improved to normal levels as early as 2 months and remained normal out to 33 months on the diet (table 2).

The family with three affected children (patients 3, 4, and 5) is of particular interest. The eldest (patient 3) had three major episodes of rhabdomyolysis and a history of multiple hospitalizations for “hypoglycemia” before diagnosis, at age 11 years. At age 13 years, patient 3 was noncompliant for a short interval. This was associated with return of muscle aches, moderate elevations of serum CPK levels (300–500 IU/L), and noticeable decreased endurance, all of which were reversed within 24 hours with resumption of the anaplerotic diet. At 44 months into the protocol, when also noncompliant, she was hospitalized after excessive sport competition. She has had no further hospitalizations out to 52 months when compliant. Her younger siblings (patients 4 and 5), at ages 7 and 10 years, had minimal symptoms at the time of entry into the diet protocol after diagnosis. After 45 months on the diet, at ages 10 and 13 years, they remain asymptomatic. Comparison of the PCS scores from the SF-36 questionnaire for these three patients shows the improvement for patient 3 compared with the normal scores both before and after the diet therapy for the two younger siblings (table 2). Longer-term evaluation might indicate some preventive value to this anaplerotic therapy that might be explored further with patients with CPT II deficiency detected by tandem mass spectrometry newborn screening.

This study reports successful management of CPT II deficiency using anaplerotic diet therapy with triheptanoin, in contrast to the patients’ previous experiences with the low-fat/high-carbohydrate diet. Further, there was no evidence of toxicity, undue weight gain, or abnormal body fat composition extending out to 61 months in any of the patients. None of these patients experienced recurrent episodes of rhabdomyolysis or required hospitalization while on the diet. Exercise restriction was eliminated, and the SF-36 scores indicated a return to a normal lifestyle without body pain.

**ACKNOWLEDGMENT**

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