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CASE REPORT

RHABDOMYOLYSIS AND MULTIORGAN FAILURE CAUSED BY CARNITINE PALMITOYL TRANSFERASE TYPE 2 DEFICIENCY

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Abstract

Background: Carnitine palmitoyl transferase 2 (CPT-2) deficiency is the most common inherited disorder of long chain fatty acid mitochondrial transport, and the cause of recurrent rhabdomyolysis in children and adults.
Case presentation: Here we present a case of a six-years-old child with severe rhabdomyolysis, where multiorgan failure (renal, hepatic, respiratory, cardiovascular, neurological) occurred and full multiple organ intensive care unit support was needed. A CPT 2 deficiency was established with genetic testing.
Conclusions: A suspicion of CPT deficit should always be present, in case of elevated levels of creatinine kinase and rhabdomyolysis, with early rehydration therapy promptly started, hemodiafiltration, respiratory and cardiovascular support if needed.

Key words: *Carnitine palmitoyl transferase; multi organ failure; rhabdomyolysis; renal failure.*

Introduction

Carnitine palmitoyl transferase 2 (CPT-2) deficiency is the most common inherited disorder of long-chain fatty acid mitochondrial transport, and the cause of recurrent rhabdomyolysis in children and adults. It is an autosomal recessive disorder.

Carnitine palmitoyl transferases are enzymes located within the walls of mitochondria. Their primary role is to transport long-chain fatty acids (LCFA) through the wall of mitochondria inside, in order for them to go through a process of ß-oxidation. This is as follows: After conjugation to coenzyme-A (CoA) with a long-chain fatty acyl-CoA synthetase, they are

transported across the mitochondrial membrane with the carnitine enzymes. CPT 1 is at the outer membrane and CPT 2 on the inner membrane. CPT 2 acts to transfer the conjugated fatty acids from carnitine within the mitochondrial matrix (1,2). After this transport LCFAs go through a process of ß oxidation, in order to get energy.

As a result of depletion of energy, due to not being able to transport LCFAs inside the cell, an increased intracellular calcium happens. This is caused by depletion of adenosine triphosphate or/ and direct injury of the plasma membrane. This leads to myocyte breakdown and release of creatinine kinase, myoglobin and electrolytes such as potassium (3).

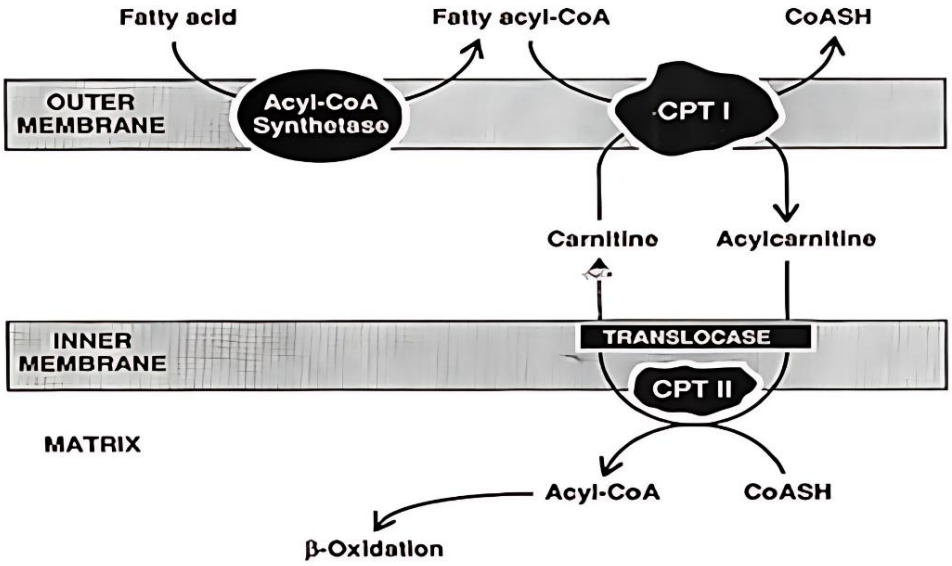

Figure 1. The mitochondrial carnitine palmitoyl transferase system, located on the mitochondrial wall, from McGarry and Brown analysis. Eur J Biochem 1997; 244 (1).

There are three variant forms of CPT II deficiency: lethal neonatal, severe infantile hepatocardiomuscular and myopathic (4). The first two present with hypoketotic hypoglycemia, liver failure, cardiomyopathy, cardiac arrythmia and peripheral myopathy. The third is the classical myopathic form which is characterized by recurrent episodes of muscle pain, muscle weakness and rhabdomyolysis triggered by exercise, stress or viruses.

Case Presentation

A six-years-old male child was admitted in the ICU, with a one-day history of fever, vomiting and diarrhea, with impaired consciousness, oligoanuria and dark urine. After admission, he was placed on oxygen support with high-flow nasal cannulas, basic and extended microbiological and biochemical analyses were taken, and rehydration therapy was initiated. However, the very next day, due to respiratory and cardiovascular failure, he was intubated and placed on mechanical ventilation and inotropic support, due to severe hypotension. Because of severe hyperkalemia, anuria and impaired peripheral perfusion, a femoral dialysis catheter (Medcomp 8F/12cm) was placed and venovenous hemodiafiltration was initiated (Prismaflex).

After microbiological analyses for a positive PCR test for Influenza type A and Varicella virus, Tamiflu and Acyclovir and broad-spectrum antibiotics were included, with systemic corticosteroid and immunoglobulins. Due to convulsive approaches, antiepileptic therapy was introduced, and a lumbar puncture was performed with a finding of viral meningoencephalitis. Because of signs of pronounced SIRS were found, an interleukin 1(IL1) blocker, anakinra, was included.

In the following period, his hemodynamics improved, and gradual weaning from catecholamine support was performed. Three weeks after starting treatment, the child began urinating again and quickly entered the polyureic phase of acute kidney injury, after which hemofiltration was stopped. A total of thirteen hemofiltration filters were used. Due to impaired consciousness and muscle weakness, a tracheotomy was performed. After that, weaning from the respirator was slowly carried out, and the child was left to breathe spontaneously in room air, with the need for aspiration of tracheobronchial secretions.

Blood was taken from the child and parents, and sent for genetic analysis, which proved the existence of a homozygous form of carnitine palmitoyl transferase type 2 deficiency. Appropriate dietary adaptation was made, and genetic counseling was performed. For the last ten days of the stay, the child was reunited with his mother, and she was trained to care for him. The child was discharged for home treatment, with a tracheostomy, due to still present muscle weakness.

Days of hospitalization	1	2	3	4	5	7	14	31	54

Leu 10^9/L 4.5-13.5	10.84	15.88	14.23	10.87	8.41	11.45	25.41	4.76	9.28
Hct %	37.4	36	31.5	33	26.6	27.6	32.8	33	39.0
Trb 10^9/L 200-436	233	127	71	44	44	51	92	174	388
CRP mg/dL 0.0-1.2/ PCT ng/ml 0-0,5	3.7/ 0.75	16.47/ >100	12.16/ >100	6.06/ >100	3.37/ >100	1.52/	1.27/ 0.89	2.13/ 0.44	0.17/ 0.08
Urea mmol/L 1.7-8.0/ Creatinine µmol/L 28-52	2.9/ 35	9.0/ 94	4.9/ 54	3.8/ 37	3.3/ 32	2.3/ 28	11.6/ 97	10.9/ 141	
Protein g/L 60-80/ Albumin g/L 38-54	72/ 45	52/ 26	49/ 31		57/ 35	63/ 35	53/ 34	57/ 35	71/ 41
AST U/L 0-40/ ALT U/L 0-41	1934/ 324	5852/ 1162	>7000/ 2853	>35000/ 2972	7541/ 2302	4281/ 2040	177/ 556	40/ 44	48/ 51
CK U/L 31-152/ CK-Mb U/L	99601/ 1645	>289546	>408480	>466339/ 12861	>331333/ 7369	>11234/ 2504	4447/ 94	160/ 55	134/ 41
Na+ mmol/L 132-145/ K+ mmol/L 3.1-5.1	131/ 4.19	135/ 6.09	135/ 3.17	135/ 3.6		133/ 4.05			141/ 4.14
INR 0.8-1.25	1.12	4.26	1.56	0.92	0.93	1.01			1.04
D-dimers µg/ml < 0.5	0.8	1.85	1.41		3.71				0.68
IL6 pg/ml 0-7		294	79.06	43.35	26.6	16.98			12
BNP pg/ml <125			51374			19703			

Table 1. Laboratory findings

Leu (leukocytes); Hct (hematocrit); Trb (thrombocytes); CRP (C-reactive protein); PCT (procalcitonin); AST (aspartate aminotransferase); ALT (alanine aminotransferase); CK (creatinine kinase); INR (international normalized ratio); IL6 (interleukin 6); BNP (B-natriuretic peptide).

Discussion

We presented a patient with fever, respiratory and heart failure and acute kidney injury, that required hemofiltration. Our patient presented severe symptoms from the beginning of the admission. Most of the other cases that we reviewed (5-15), suggest a risk of developing a renal failure, and also generate a hypothesis that the CK levels on admission were connected with early organ support (16). However, this requires further directed study in order to prove this.

As we can see from the laboratory findings, on the first day of admission, they indicated elevated creatinine kinase (CK) and CK-Mb, but the whole picture was shown on the second and the next consecutive days. The levels of CK were the highest on the fourth day >466 339, which suggested massive rhabdomyolysis and no wonder an acute kidney injury occurred. These high levels of CK were not presented in the other case reports we reviewed (5-15).

The clinical condition worsened on the second day, despite rehydration therapy, with acute hyperkalemia and anuria, when hemofiltration was started. The urea and creatinine levels were normal most of the time, but that is due to hemofiltration. The patient was anuric for three weeks. After that the renal function was normalized and needed no support.

The patient's condition was very bad not only due to the rhabdomyolysis, but also due to the intense systemic inflammatory response syndrome, manifested as profound hypotension which required high doses of inotropes, systemic glucocorticoids and IL1 blocker.

Children tend to develop symptoms from more organ systems, such as fever, convulsions, anuria, respiratory insufficiency and multiple organ dysfunction, as our patient did, compared to adults where they mostly develop myalgia and sometimes renal symptoms (17). Also, one case report described CPT 2 deficiency in 13-years-old girl, which resulted in death due to hyperkalemia, renal failure, hypertension and life-threatening arrhythmias (18).

Scharman et al. (19) believed that early fluid resuscitation within the first 6 hours of muscle injury can reduce the occurrence of acute renal failure. In this paper, all 4 cases of rhabdomyolysis induced by exercise showed myalgia and tea-colored urine after exercise (squats, frog jumps, long-distance running). None of them developed acute renal failure, which may be related to timely medical treatment and early treatment, small lesion range (limb muscle injury), no chronic disease and good organ function.

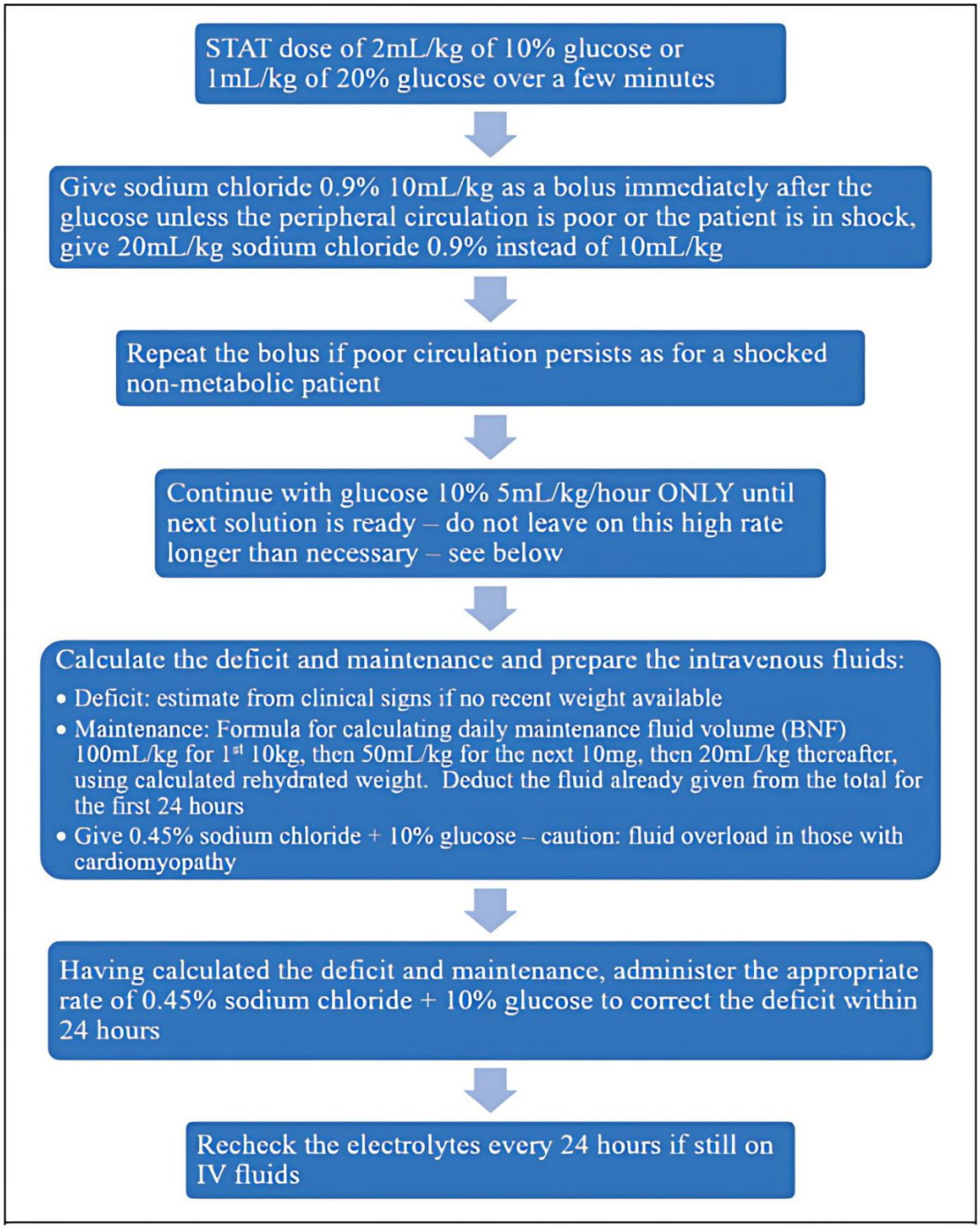

Figure 2. Intravenous glucose management in acute rhabdomyolysis in acutely decompensated LCFA disorders, from the British Inherited Metabolic Disease Group (20).

Establishing the diagnosis of CPT 2 deficiency, can be done with acylcarnitine analysis with tandem mass spectrometry. Also, laboratory findings, such as increased serum plasma creatinine kinase, transaminases, low carnitine levels, are found in these patients. But a definitive diagnosis is made with sequencing of the CPT2 gene for mutation analysis.

Long-term treatment is mainly based on an adapted diet: Avoidance of fasting, high-carbohydrate and low-fat diet, frequent meals, supplementation with medium-chain fatty acids and carnitine. Also, prevention should be emphasized, such as protection from infections, stress, prolonged exercise, exposure to cold, fever, fasting and prohibition of some medications (ibuprofen, valproic acid). The medium-chain fatty acid triheptanoin has been described to be effective in the late-onset CPT II deficiency (21).

Conclusion

A suspicion of carnitine palmitoyl transferase deficit should always be present, in case of elevated levels of creatinine kinase and rhabdomyolysis. Early rehydration therapy should promptly be started. If the symptoms are worsening, these patients need to be placed in an intensive care unit setting, in order to start early with adequate support, such as hemodiafiltration, respiratory and cardiovascular support.

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