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CASE REPORT

Rhabdomyolysis and respiratory failure: rare presentation of carnitine palmityl-transferase II deficiency

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ABSTRACT

Carnitine palmityl-transferase (CPT) II deficiency is a rare disorder of the fatty acid beta-oxidation cycle. CPT II deficiency can be associated with rhabdomyolysis in 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. The best known CPT II deficiency is the muscular form with episodic muscle necrosis and paroxysmal myoglobinuria after prolonged exercise. We report a case of a four-year-old male child, who, after one day of hyperthermia and fasting, developed a massive rhabdomyolysis beginning with acute respiratory failure and later complicated by acute renal failure. Appropriate management in Pediatric Intensive Care Unit (PICU) (mechanical ventilatory support, fluid supply combined with mannitol and bicarbonate infusions, administration of acetaminophen and antibiotics, and continuous venovenous haemofiltration) brought about complete resolution with an excellent outcome. Biochemical investigation of muscle biopsy and genetic analysis showed a deficiency of CPT II. The onset of CPT II deficiency with respiratory failure is extremely rare, but a correct and early diagnosis of rhabdomyolysis is the key to successful treatment. A metabolic myopathy such as CPT II deficiency should be suspected in children affected by rhabdomyolysis if trauma, crash, infections, drugs or extreme exertion can be excluded.

Key words: Carnitine-palmityl-transferase - Rhabdomyolysis - Respiratory insufficiency - Kidney failure, acute - Biopsy, needle.

The carnitine palmityl-transferase (CPT) II enzyme is responsible for the hydrolysis of the long-chain fatty acid bound to carnitine following transport across the intermitochondrial membrane. CPT II deficiency is a rare disorder of the fatty acid beta-oxidation cycle with heterogeneous phenotypes and occurs secondarily to either alpha or beta subunit mutations.[1] The incidence of the disease has been reported to be between 1 in 15 000 and 1 in 30 000 births.

CPT II deficiency can produce distinct clinical presentations. The best known is the muscular form with episodic muscle necrosis and paroxysmal myoglobinuria after prolonged exercise in young adults.[2-4]

We report a case of massive rhabdomyolysis starting with acute respiratory failure and later complicated by acute renal failure in a child affected by CPT II deficiency.

Case report

A four-year-old male weighing 18 kg was admitted to the Pediatric Intensive Unit (PICU) after a day of hyperthermia (>39 °C) and fasting with myalgia, generalized muscular weakness, worsening respiratory failure, lethargy and extremely dark coloring of urine. At the time of admission the respiratory rate was 64 breaths/min, and arterial blood gas values were pH 7.25, pCO_2 95 mmHg, pO_2 61 mmHg, HCO_3 39 mEq/L without parenchymal pulmonary abnormalities in chest radiograph. Heart rate and blood pressure were 154

TABLE I.—*Trend of creatinine, Mb and CPK values in relation to course of respiratory parameters during the period of ICU-stay.*

	1st day	2nd	3rd	4th	5th	6th	7th	10th	12th
Creatinine (mg/dL)	2.9	3.8	4.6	1.8	1.6	2.7	2.4	1.8	1.5
Mb (μg/L)	62.220	38.200	31.270	20.650	14.530	11.941	3.732	540	45
CPK (U/L)	320.000	250.300	143.400	78.630	57.200	19.430	6.570	540	204
Renal support	—	—	CVVH	CVVH	CVVH	—	—	—	—
$PaCO_2$ (mmHg)	95	34	38	65	61	47	37	41	39
RR (breaths/min)	64	22	22	49	48	40	28	24	19
VT (mL/kg)	—	8	8	4	4	4	7	—	—
RSB (RR/VT)	—	2.7	2.7	12.2	12	10	4	—	—
Weaning test	—	—	—	WT	WT	WT	WT	—	—
Ventilation	SB	PCV	PCV	PCV	PCV	PCV	PSV	SB	SB

CVVH: continuous veno-venous haemofiltration; PCV: pressure control ventilation; PSV: pressure support ventilation; WT: weaning test; SB: spontaneous breathing. The values of the 1st day were collected on admission to PICU The respiratory parameters of the 2nd and 3rd days were collected during PCV. The respiratory parameters of the 4th, 5th and 6th days were collected after 30 minutes of the weaning test. The values of the 12th day represent the pre-discharging condition from the PICU.

beats/min and 95/67 mmHg, respectively. Diuresis in the first six hours was 0.8 mL/kg/h. Blood analysis yielded the following results: myoglobin (Mb) 62.220 g/L, creatine phosphokinase (CPK) 320.000 U/L, CPK isoenzyme muscle-brain 327 U/L, aspartate aminotranferase (AST) 3.931 U/L, alanine aminotransferase (ALT) 960 U/L, creatinine 2.9 mg/dL, urea 11 mg/dL, glycemia 149 mg/dL, hemoglobin 12.6 g/dL, white blood cells count 9.1×10^{-3}, C-reactive protein (CPR) 2.37 mg/dL, interleukine-2-receptor 1.730 UI/L, and interleukine-6 8.7 pg/mL. Urine analysis showed myoglobinuria 12.500 g/L. The PRISM (Pediatric RISk of Mortality) score was 13.

The patient was immediately given mechanical ventilatory support, a fluids supply (85 mL/kg/day) combined with mannitol (0.5 g/kg/dose) and bicarbonate infusions (to a urine pH level >6.5), administration of acetaminophen (20 mg/kg/dose), antibiotics (ceftriaxone 50 mg/kg/day) and sedative (midazolam 1 g/kg/min).

After 24 hours the hemogasanalytic values were normal, and diuresis was 2.1 mL/kg/h, but Mb (38.200 g/L), CPK (250.300 U/L), AST (4.408 U/L), ALT (1261 U/L) and creatinine (3.8 mg/dL) remained high.

Echocardiography excluded cardiac and hepatic abnormalities. Neurological examination disclosed marked weakness of all major muscle groups without focal signs.

The parents reported that ten months previously, the child had suffered from an attack of muscle stiffness and myalgia after hyperthermia; the symptoms had disappeared after a few hours and the child's doctor was not unduly concerned.

Forty-eight hours after admission to the PICU, a progressive oligoanuria associated with an increase in creatinine was observed while values of Mb and CPK remained constantly high. These clinical features, suggestive of an acute renal failure due to acute tubular necrosis, prompted us to perform continuous venovenous hemofiltration (CVVH).

Microbiological tests provided no evidence of active infection from bacterial or viral agents including: *Streptococcus Pneumoniae, Mycoplasma Pneumoniae*, *Legionella, Influenza A* and *B*, *Parainfluenza* types *1, 2* and *3*, *Herpesvirus, Respiratory Synctial Virus, Adenovirus, Cytomegalovirus,* and *Echovirus.* Because of these negative results, the empiric antibiotic therapy, started because of hyperthermia and high white blood cells count, was discontinued after the third day.

CVVH was continued for three days and mechanical ventilatory support for seven days (six with pressure control ventilation, one with pressure support ventilation). From the fourth day after admission to the PICU, some attempts at weaning from the ventilator were made, and this goal was finally achieved 6 days after admission. The patient was extubated after seven days when the Mb and CPK values had fallen to below 6.000 g/L and 10.000 U/L, respectively. The course of creatinine, Mb and CPK values during the period of ICU-stay in relation to renal support, weaning and respiratory muscle function are shown in Table I. We considered some parameters describing gas exchange, such as $PaCO_2$, and the respiratory functionality, such as the spontaneous respiratory rate (RR_S), spontaneous tidal volume (TV_S) and pediatric rapid shallow breathing (RSB),[5] that represents the ratio between RR_S and TV_S with a normal value <10. The course of Mb and CPK values from the third to seventh day in relation to RSB are shown in Figure 1.

The patient underwent physiotherapy, which aided the progressive recovery of muscle strength. The child stayed in PICU for twelve days and was discharged from hospital 28 days after admission.

Muscle biopsy, performed 35 days after the acute episode, revealed fibres with regular structure and normal size and without degeneration or necrosis. Biochemical investigation of the muscle showed deficiency of CPT II activities with a value of 0.6 nmol/min/mg (mean value 10-14). Genetic analysis confirmed the diagnosis of CPT II deficiency. Despite the initial severe condition, the final outcome was excellent.

Discussion

Muscle CPT II deficiency is a disorder of fatty acid oxidation, often characterized by attacks of myalgia and myoglobinuria.[2]

Three distinct clinical entities have been described: the perinatal, infantile and adult forms, all with an autosomal recessive inheritance pattern. The perinatal form is the most severe and is invariably fatal. The infantile forms frequently involve multiple organ systems. Adult deficiency is somewhat benign and requires additional external triggers such as high-intensity exercise before the predominantly myopathic symptoms are elicited.[3, 4, 6]

CPT II deficiency can be associated with rhabdomyolysis following 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.

Rhabdomydysis occurs after insults that trigger perturbations in intracellular calcium flux. The subsequent release of intracellular contents from dead or dying myocytes leads to extreme perturbations in the normal physiology and myoglobin release.

Apart from metabolic and hereditary diseases, such as CPT II deficiency, rhabdomyolysis may be caused by a variety of mechanisms affecting the myocytes and muscle membranes and should always be considered as a differential diagnosis of trauma, generalized seizures, drugs, toxic substances, infectious agents, and hyperthermic syndromes.[7, 8]

The severity of the systemic metabolic derangement produced during rhabdomyolysis depends on both the extent of muscle damage and potentiating factors such as hypotension, hypovolemia, electrolyte abnormalities, extremes of body temperature, age and genetic predisposition to muscle injury. Acute renal failure is both the most frequent and serious complication of rhabdomyolysis. Mb is responsible for renal dysfunction due to renal vasoconstriction, tubular damage and tubular obstruction. Much more rarely, extensive and progressive myopathic involvement of the respiratory muscles may lead to acute ventilatory failure.[7-9]

In this paper, we report the case of a child with CPT II deficiency who presented a respiratory failure as the first, acute, atypical and dangerous symptom of rhabdomyolysis. The high value of Mb, CPK and myoglobinuria easily led us to a diagnosis of rhabdomyolysis, whereas it was harder to identify the underlying pathology that had triggered this condition. The exclusion of trauma, crash, severe infections, extreme exertion, or ingestion of drugs or toxic substances led us to consider the hypothesis of a metabolic disease. This was supported by an anamnestic report of a previous episode of muscular stiffness and myalgia after hyperthermia, despite a lesser severity. In this setting, the most probable hypothesis was a metabolic disease concerning genetic defects of fatty acid oxidation, bearing in mind that the diagnosis can be confirmed exclusively with muscular biopsy, but this would have been possible and reliable only after resolution of the acute phase of muscular damage.

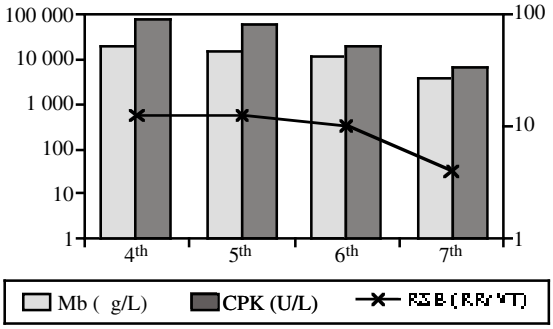

Figure 1.—Trend of RSB in relation to Mb and CPK values from 4th to 7th day of admission to the PICU.

In the clinical history of the patient, hyperthermia and prolonged fasting (almost 24 hours in a child of 4 years) appear to have been concomitant factors that triggered the clinical picture in the context of serious CPT II deficiency. A third event, such as a slight infection, enhanced by hyperthermia and the values of white blood cells, CPR and interleukine-2-receptor could also be considered, even though no evidence of infectious agents was found in the present case.

The combined treatment for hypoventilation and renal failure constituted the main elements of the therapy. In paediatric age renal replacement therapy and mechanical ventilatory management are based on well-defined clinical and laboratory procedures, all of which were respected in this case.[10]

A question arising during the respiratory treatment of this child was whether during massive rhabdomyolysis a correlation could exist between

the muscle efficiency, with the possibility of successful respiratory weaning, and the laboratory values of skeletal muscle cell damage, such as hematic Mb and CPK. There are no references to this issue in the literature, but it is notable in the present case that adequate respiratory function reached stability only when the levels of Mb and CPK, initially very high and indicating extensive muscle injury, had fallen dramatically with respect to those at the start of the acute episode. In other words, our data suggest that the recovery from the respiratory insufficiency was somehow related to the reduction in the severity of the rhabdomyolysis.

Conclusions

The onset of CPT II deficiency with respiratory failure is extremely rare, just as the presence of severe respiratory failure associated with rhabdomyolysis is by no means usual. The correct and early diagnosis of rhabdomyolysis is the key to successful treatment and prevention of possible complications.

A metabolic myopathy such as CPT II deficiency should be suspected in children affected by rhabdomyolysis if trauma, crash, severe infections, drugs or extreme exertion can be excluded and if there is a history of episodes of muscle weakness. Genetic, tissue and biochemical analysis are necessary for diagnosis and screening.

References

1. Cwik VA. Disorders of lipid metabolism in skeletal muscle. Neurol Clin 2000;18:167-84.
2. David WS. Myoglobinuria. Neurol Clin 2000;18:215-43.
3. Bonnefont JP, Djouadi F, Prip-Buus C, Gobin S, Munnich A, Bastin J. Carnitine palmitoyltransferases 1 and 2: biochemical, molecular and medical aspects. Mol Aspects Med 2004;25:495-520.
4. Katzir Z, Hochman B, Biro A, Rubinger DI, Feigel D, Silver J *et al.* Carnitine palmityltransferase deficiency: an underdiagnosed condition? Am J Nephrol 1996;16:162-6.
5. Baumeister BL, El Kathib M, Smith PG, Blumer JL. Evaluation of predictors of weaning from mechanical ventilation in pediatric patients. Pediatr Pulmonol 1997;24:344-52.
6. Kilfoyle D, Hutchinson D, Potter H, George P. Recurrent myoglobinuria due to carnitine palmitoyltransferase II deficiency: clinical, biochemical, and genetic features of adult-onset cases. N Z Med J 2005;25:1320.
7. Brumback RA, Feeback DL, Leech RW. Rhabdomyolysis in childhood. Pediatr Clin North Am 1992;39:821-58.
8. Warren JD, Blumbergs PC, Thompson PD. Rhabdomyolysis: a review. Muscle Nerve 2002;25:332-47.
9. Bertorini T, Yeh Y, Trevisan C, Stadlan E, Sabesin S, Di Mauro S. Carnitine palmityl transferase deficiency: myoglobinuria and respiratory failure. Neurology 1980;30:263-71.
10. Holt S, Moore KP. Pathogenesis and treatment of renal dysfunction in rhabdomyolysis. Int Care Med 2001;27:803-11.

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