

Reversible asphyxial status in a newborn due to neonatal form of carnitine palmitoyltransferase II deficiency

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Abstract

OBJECTIVES: To present a term newborn with severe asphyxial status due to dysrhythmia induced by the neonatal form of carnitine palmitoyltransferase II deficiency (CPT II).

RESULTS: Term newborn delivered spontaneously (birth weight 3450 grams, birth length 52 cm, values of Apgar score 10/10) with good direct adaptation, on second day of life he manifested severe asphyxial status followed by cardiorespiratory insufficiency with circulatory failure. After prolonged resuscitation of 3 hours, the child was admitted to our neonatological department. Diagnosis of CPT II was confirmed (free carnitine level in blood 12.2 $\mu\text{mol/l}$; ratio (C16+C18):1/C2 was 0.760 by tandem mass spectrometry; activity of CPT II in leukocytes was 0.082 $\mu\text{mol/min} \times \text{gram protein}$). After appropriate treatment the patient survived the critical period.

CONCLUSIONS: Neonatal form of CPT II deficiency is the most severe form and is considered to be invariably fatal. This kind of metabolic disease is congenital, but cardiac problems are not detectable during the prenatal period. Fasting in the early newborn period is a main trigger of CPT II deficiency signs. The authors emphasise the relevance of investigating acylcarnitine profiles and carnitine in serum in all cases of severe postnatal asphyxia and in cases of unusual newborn arrhythmias since some forms of disturbances in β oxidation of fatty acids are partially treatable.

Abbreviations

CoA	- coenzyme A
CPT	- carnitine palmitoyltransferase
CPT I	- carnitine palmitoyltransferase I
CPT II	- carnitine palmitoyltransferase II
LCFA	- long chain fatty acids

INTRODUCTION

Utilisation of fat as a long-term energy storage vehicle is crucial for the maintenance of cellular metabolism. Without the body's ability to convert fat into energy for muscle movement or glucose, which is needed by the brain, or amino acids that are required for the maintenance of all biological processes, we would perish (Bebernitz and Schuster, 2002).

Mitochondrial fatty acid oxidation constitutes the main energy supply for the liver, heart, and skeletal muscle in situations that require mobilisation of endogenous glucose, such as fasting, prolonged exercise, and in the early neonatal period (Brucknerová *et al.*, 2006; Ujházy *et al.*, 2006). The primary pathway for oxidation of fatty acids occurs in the mitochondria although alternate oxidation pathways exist in peroxisomes and in the endoplasmic reticulum. The movement of long chain fatty acids into mitochondria requires the use of a specific carnitine transport system referred to as carnitine palmitoyltransferase (CPT). CPT system consists of three enzymes located in the outer (carnitine palmitoyltransferase I, CPT I) and in the inner (translocase and carnitine palmitoyltransferase II, CPT II) mitochondrial membranes. They catalyse the same reaction but in opposite directions. CPT I converts the coenzyme A (CoA) esters of long chain fatty acids into their respective carnitine esters. It has three isoforms – liver, muscle and brain. Translocase transports these carnitine esters to the inner mitochondrial matrix. CPT II converts the carnitine esters back into its CoA esters. These CoA esters are then processed by β oxidation pathways. CPT II is ubiquitous in the human adult (Bebernitz and Schuster, 2002).

Deficiency of CPT II is the most common autosomal recessive disorder of mitochondrial beta-oxidation of long chain fatty acids (LCFA). LCFA-carnitine esters are translocated across the inner mitochondrial membrane but are not processed into their CoA esters (in contrast to medium-chain and short-chain fatty acids LCFA require a CPT system to enter the mitochondrial matrix). Deficiency of CPT II has a fascinating phenotypic variability. The group of main triggers involves fasting, high intensity exercise and severe infection.

The clinical manifestation of CPT II deficiency has 3 forms. The first one, called **neonatal form**, is the most severe form and invariably fatal, and is characterized by hypoketotic hypoglycaemia, dysmorphic features, cystic renal dysplasia, neuronal migration defects and sudden death (Demaugre *et al.*, 1991). The second one

is the **early onset infantile form**, called “**hepatocardiomyopathy**”. It is characterised by acute liver failure, hypoketotic hypoglycaemia, coma, seizures, transient hepatomegaly, cardiomyopathy and peripheral myopathy. Both forms are life-threatening diseases and patients usually die during the first months of life (Vekemans *et al.*, 2003). The third one is the **late onset adult muscular form** characterised by episodes of muscle pain, muscle weakness and rhabdomyolysis triggered by prolonged exercise (DiMauro and DiMauro, 1973). It is the most frequent form.

CASE REPORT

Our patient was a first term male newborn of unrelated parents of Caucasian origin, delivered spontaneously with birth weight 3450 grams, birth length 52 cm, values of Apgar score 10/10, appropriate for gestational age, with good direct postnatal adaptation, and dysmorphic features. On the 2nd day of life, after recurrent vomiting, bradycardia was followed by severe asphyxial status due to dysrhythmia followed by cardiorespiratory insufficiency with circulatory failure. After 3 hours of prolonged resuscitation the child was admitted to our intensive care unit. The patient was on mechanical ventilatory support, hibernated for 72 hours.

Laboratory findings at the time of admission confirmed severe metabolic acidosis (pH 7.19, base excess -16.4) and elevated serum values of hepatic enzymes aspartate aminotransferase 24.62 μ kat/l (normal value 0.8 \pm 0.12 μ kat/l) and alanin aminotransferase 9.97 μ kat/l (normal value 0.29 \pm 0.04 μ kat/l). There were no signs of inflammation. Ultrasonic investigation of the heart excluded structural congenital disease. Aspiration and paroxysmal supraventricular tachycardia were not confirmed. Ultrasonic investigation of the brain parenchyma confirmed atrophy of the brain, diffuse hypoxic-ischaemic changes, presence of post-haemorrhagic lesions in choroid plexus and dilatation of the lateral ventricles and the third ventricle. Diagnosis of metabolic disease was based on investigation of free carnitine in blood (12.3 μ mol/l; normal value: 24.3–62.5 μ mol/l) and of long-chain acylcarnitines C10–C18, mainly (C16+C18):1/C2 ratio (0.760; normal value: 0.011–0.048) by tandem mass spectrometry. Reduced activity of CPT II in leukocytes (0.082 μ mol/min \times gram protein; normal values: 1.0–4.5) was confirmed. Activity of the transport control measured in parallel was 4.5 μ mol/min \times gram protein. Sequencing of the whole CPT II gene revealed a heterozygous 1237delAG+F448L mutation.

DISCUSSION

Congenital deficiency of CPT II has been known for at least 30 years and its phenotypic variability remains fascinating. Carnitine palmitoyltransferase II defi-

ciency is an autosomal recessive disorder of mitochondrial β oxidation of fatty acids. Three phenotypes are described: neonatal (perinatal), infantile and adult form (Vekemans *et al.*, 2003; Smeets *et al.*, 2003). The distinct clinical phenotypes of CPT II deficiency correlate in some extent to distinct genotypes (Bonnet *et al.*, 1999). Neonatal and infantile forms are life-threatening diseases, patients usually die during the first months of life (Vekemans *et al.*, 2003). The reason for sudden death is arrhythmia secondary to metabolic cause, which is more common than primary rhythm disorders (Banani *et al.*, 2006).

Smeets *et al.* (2003) described a Moroccan family whose four out of five children had died from neonatal form of CPT II deficiency. Vekemans *et al.* (2003) described two patients with neonatal CPT II deficiency. The first patient died at 22 months of age of gastroenteritis episode, the second during a viral episode. Both were presented with typical signs of neonatal form of CPT II deficiency. Of the cardiovascular signs, the bradycardia at 4 hours of life with hypoglycaemia was present in both patients. Hypertrophic cardiomyopathy developed later. Both children died despite the nocturnal enteric feeding of medium-chain triglycerides-enriched and long-chain fat restricted carbohydrate diet. A further term newborn with CPT II deficiency with bradycardia on the second day of life was described by Albers *et al.* (2001). The patient died on the third day of life due to severe arrhythmic episodes and blood pressure instability.

Sharma *et al.* (2003) presented a male newborn, comparable with our patient, appropriate for gestational age, with severe cardiac dysrhythmia within 24 hours. Prenatally cystic renal dysplasia without oligohydramnios was identified. Postnatally gradual hypotonia, lethargy, and poor feeding developed and by 20 hours of age recurrent cardiac dysrhythmia, myocardial dysfunction, and renal insufficiency with intermittent hyperkalaemia were apparent. The patient died at the age of 12 days. Lethal neonatal CPT II deficiency was confirmed by autopsy.

Our patient with neonatal form of CPT II deficiency has survived despite severe postnatal asphyxial status due to serious rhythm disturbances, with prolonged resuscitation (3 hours) during the third day of life. We agree with Bonnet *et al.* (1999) that the accumulation of arrhythmogenic intermediary metabolites of fatty acids, such as long-chain acylcarnitines, may be responsible for arrhythmias. In comparison to patients described by Bonnet *et al.* (1999), no patient with CPT II deficiency had bradycardia, as was the case in our patient. During the whole further period of development normoglycaemia was maintained. It was achieved by using a low fat diet with high caloric intake, maltodextrin, MCT oil, L-carnitine, essential amino acids and polyvitamins. Problems with feeding required a nasogastric tube and at the age of 4 months percutaneous endoscopic gastrostomy. At present, the patient is

4 years old without rhythm disturbances, without signs of cardiomyopathy.

Prevention of long-chain acylcarnitine accumulation is probably a promising approach to the prevention of sudden cardiac death. The slowly improving neurological status of our patient displays delayed psychomotor development, peripheral hypertonia and axial hypotonia.

Prenatal diagnosis by DNA isolation from chorionic villi is possible at 10 weeks of gestation. At least 40 different mutations have been identified and reported, but genotype-phenotype correlations remain unclear (Thuillier *et al.*, 2003; Bonnet *et al.*, 1999). Intrafamilial phenotypic homogeneity is a common feature of neonatal and infantile forms of CPT II deficiency.

CPT II activity could be assayed on cultured amniocytes between 16–17 weeks of gestation (Vekemans *et al.*, 2003). The mother of our patient will be called for prenatal DNA analysis during her next pregnancy.

CONCLUSION

Utilisation of fat as a long-term energy storage vehicle is crucial for the maintenance of cellular metabolism. The neonatal form of CPT II deficiency is the most severe form and is considered invariably fatal. This kind of metabolic disease is congenital, but the cardiac problems are not detectable during the prenatal period. Fasting in the early newborn period is a main trigger of CPT II deficiency manifestations. In differential diagnosis of cardiac failure of unknown etiology infection, congenital heart disease, aspiration, heart rhythm disturbances have to be excluded. The authors point out that in differential diagnosis of cardiac failure in neonatal age one of its possible cases can be an unrecognised metabolic disease, particularly disturbance in β oxidation of fatty acids. The authors emphasise that investigation of long-chain acylcarnitines and carnitine in serum is important and useful because some forms of disturbances in β oxidation of fatty acids are partially treatable. They point out the relevance of performing neonatal metabolic screening of acylcarnitine profiles in all cases of unusual newborn arrhythmias and corresponding analysis of postmortem specimens in cases of sudden death syndrome.

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