

# Carnitine-acylcarnitine translocase deficiency

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**Creation Date: April 2001**

**Update: October 2004**

**Scientific Editor: Professor Jean Marie Saudubray**

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## Abstract

*Carnitine-acylcarnitine translocase (CACT) deficiency is an autosomal recessive disorder of long chain fatty acid oxidation. The carnitine-acylcarnitine carrier is an inner mitochondrial membrane protein that catalyzes the mole-to-mole exchange between internal carnitine and external acylcarnitines. Human CACT has been cloned, the structure and the organization of the gene elucidated. CACT deficiency is a severe disease that can cause neonatal or infantile sudden death. About 30 cases of this disorder have been reported. In most patients the presenting features were neonatal neurological distress (lethargy, poor feeding), cardiac rhythm disorders and hypoketotic hypoglycemia with hyperammonemia. Hepatomegaly and hypertrophic cardiomyopathy may develop secondarily. Urine organic acids are more or less informative for the biological diagnosis. Determination of the blood acylcarnitine profile and in vitro fatty acid oxidation studies in lymphocytes or fibroblasts are the two main ways to establish the diagnosis, which can be confirmed by the specific determination of carnitine-acylcarnitine exchange in digitonin-permeabilized cells. Treatment mainly involves the blockade of lipolysis and avoiding fasting by glucose infusion or frequent meals and nocturnal nasogastric feeding with a high-carbohydrate / low-fat diet. L-Carnitine supplementation is now also considered helpful. Long chain fatty acid intake should be restricted and medium chain triglycerides should be used instead. Prenatal diagnosis is available by enzymatic or molecular analyses.*

## Keywords

Fatty-acid oxidation; carnitine; acylcarnitines; hypoglycemia; hyperammonemia; sudden infant death

## Disease name and synonyms

Carnitine-acyl carnitine translocase deficiency (CACT deficiency),  
Carnitine-acylcarnitine carrier deficiency.

## Diagnostic criteria/definition

CACT deficiency is a long-chain fatty acid oxidation disorder characterized by life-threatening events occurring during the neonatal period, when a rapid adaptation to lipids as the

essential metabolic fuel is necessary for the newborn. Neurological distress (lethargy, poor feeding) and cardiac rhythm disorders are the main presenting clinical features associated with hypoketotic hypoglycemia and hyperammonemia. CACT deficiency can cause of neonatal or infantile sudden death.

### Differential diagnosis

Three main differential diagnoses must be considered.

#### Urea cycle defects

Neonatal neurological distress and hyperammonemia are common symptoms of patients with either a CACT deficiency or a urea-cycle defect. Hypoglycemia, negative designation of trace ketonuria by acetest and dicarboxylic aciduria are indicative of a fatty acid oxidation defect. Plasma amino acid levels and urine orotic acid concentration are useful to exclude defects of ornithine trans-carbamylase, argininosuccinate synthetase or lyase and arginase. However, they do not provide information regarding the possible defects of N-acetylglutamate synthetase or carbamylphosphate synthetase, which can only be assessed in a liver biopsy. Determination of the plasma acylcarnitine profile by tandem mass spectrometry and *in vitro* fatty acid oxidation studies in lymphocytes or fibroblasts are helpful to rapidly confirm or exclude a defect of long chain fatty acid entry into mitochondria.

#### Neonatal infections

Because neonatal infections are more frequent causes of life-threatening events in the neonates than fatty acid oxidation defects, neonatologists must be aware of their possible occurrence and perform an urgent metabolic work-up, particularly in consanguineous families.

#### Other defects of long chain fatty acid oxidation

This differential diagnosis is less important for the management of patients, since it does not imply a different therapeutic approach. Patients with carnitine-palmitoyl transferase type II deficiency, very long chain acylcoenzyme A (acylCoA) dehydrogenase deficiency or mitochondrial trifunctional protein deficiency present with clinical features similar to those of patients with CACT deficiency. Urine organic acid chromatography, tandem mass spectrometry, determination of the plasma acylcarnitine profile and *in vitro* fatty acid oxidation studies may contribute to the recognition of the defect before scheduling a specific enzyme assay.

### Prevalence

Among the disorders of fatty acid oxidation, CACT deficiency is one of the rarest; 30 cases have been reported (1-21).

### Clinical description

The metabolic block in this disorder results in defective intramitochondrial transport of long chain acylcarnitines which, in turn, causes ineffective mitochondrial  $\beta$ -oxidation and ketogenesis. As energy metabolism in neonates mainly relies on long-chain fatty acid oxidation, most reported patients had an acute onset within the first hours of life. Seizures, neurological distress, cardiac beat disorders, and/or apnea have been reported as the presenting features associated to hypoglycemia with no ketone bodies in urine, hyperammonemia, minor rhabdomyolysis and sometimes hypocalcemia. Hepatomegaly, hypertrophic cardiomyopathy, muscle weakness and multiorgan failure may develop secondarily. Fourteen reported cases were fatal. Two patients survived beyond six months but experienced subsequent episodes of acute decompensation after fasting and died in early childhood (11,18). Twenty-one older siblings of the index patients had died unexpectedly in infancy. There have been only seven reports of mild phenotypes (7-10,14,16), which seems to correspond to residual enzyme activity, but the degree of neonatal lipolysis is another important determinant of the clinical outcome as exemplified by the case of a boy with residual activity equal to 5% of control values which sufficed for a normal growth and development at 3 years of age (9). After the previous deaths of two siblings during infancy, this boy was immediately breast-fed at birth and given supplements of milk formula through a nasogastric tube in order to block lipolysis. This treatment enabled him escape to acute neonatal decompensation.

### Management including treatment

As soon as a fatty acid oxidation disorder is suspected, the most important goal is to provide sufficient glucose to prevent adipose tissue lipolysis. Delay may result in sudden death, cardiac arrhythmia, collapse or permanent brain damage.

This objective can be met by infusing 10% glucose at rates of 10-12 mg/kg/min or more to maintain high to normal plasma glucose levels > 5 mmol/L. This infusion is difficult to perform in a peripheral vein. A central line catheter should be installed and later a porta cath catheter for easy access in case of an emergency. Even better control of neonatal lipolysis may be

obtained with simultaneous use of insulin and glucose.

When there is no vomiting and no diarrhea, a 10-15% glucose polymer solution through a nasogastric drip alone or in combination with intravenous infusion may be used.

Long chain fatty acid intake should be restricted and MCT (medium chain triglycerides) should be used instead. Since the C10 fatty acids mitochondrial transport depends on carnitine (4,16) and some MCT oil formulas contain high percentage of C10 fatty acids, low C10 fatty acids oil formulas should be preferred (21,22)

L-Carnitine therapy is mandatory to counter the defects of long chain fatty acid entry into mitochondria (100-200 mg/kg/day intravenously for an emergency, then given orally 3-4 times a day). Carnitine therapy has long remained controversial because of a theoretical risk of acute accumulation of long-chain acylcarnitines, which were found to be arrhythmogenic in experimental situations. However, it is very well tolerated and helpful. Carnitine probably acts by lowering the accumulation of acylCoA and restoring the CoA pool in mitochondria.

The long-term strategy includes maintenance of high carbohydrate/low fat diet supplemented with essential polyunsaturated fatty acid. Fasting should be avoided by frequent meals (every 3 hours) and addition of continuous naso-gastric feeding. Ingestion of uncooked cornstarch at bedtime could be an alternative.

### Etiology

CACT deficiency is an autosomal recessive disorder affecting the entry of long chain fatty acids into the mitochondria. Long-chain fatty acids destined for  $\beta$ -oxidation enter mitochondria bound to carnitine. Before entering mitochondria, acyl groups are transferred from CoA to carnitine by the outer membrane carnitine palmitoyltransferase I (CPT I). Carnitine acylcarnitine translocase CACT catalyzes the movement of acylcarnitines across the inner mitochondrial membrane in exchange for free carnitine. After entering the mitochondria, acyl groups are transferred back to CoA by the inner membrane carnitine palmitoyltransferase II (CPT II) and the resulting acylCoAs are subjected to the process of chain shortening. CACT is an inner mitochondrial membrane carrier protein. Human CACT has been cloned and the gene mapped to chromosome 3p21.31 (25). The structure and organization of the gene have been elucidated (23) and various mutations have been described (24-29,6-8,19,21).

### Diagnostic methods

Gas chromatography-mass spectrometry analysis of urine organic acids may reveal mild principal findings that are suggestive of either CPT II or CACT deficiency :

1- severe plasma free carnitine deficiency associated with a high level of acylcarnitines (up to 90% of total plasma carnitine);

2- profile of long chain fatty acid derivatives with large amounts of C16:0, C16:1, C18:1, C18:2 species, revealed by quantitative tandem mass spectrometry analysis of acylcarnitines in blood or plasma samples;

3- marked reduction of *in vitro* long chain fatty acid oxidation in lymphocytes or fibroblasts.

The definitive diagnosis is made by using a coupled assay measuring [ $^{14}$ C] acetylcarnitine/L-carnitine exchange through the mitochondrial membranes of digitonin permeabilized cells (lymphocytes, cultured fibroblasts) ;

[ $^{14}$ C] acetylcarnitine is produced inside the mitochondria from [ $^{14}$ C<sub>2</sub>] pyruvate (11). Fresh cells are needed for this assay, which cannot be run on a frozen tissue.

In case of sudden neonatal or infantile death highly suggestive of a long-chain fatty acid oxidation disorder, postmortem examinations of tissue and body fluids may give clues to the diagnosis:

1-lipid infiltration of liver, skeletal and myocardial muscles or kidneys is indicative of a fatty acid oxidation disorder,

2-an abnormal acylcarnitine profile with the accumulation of C16, C18 species in a blood spot on a Guthrie card or in bile should prompt the search for a CPT II or a translocase defect.

However, if a fibroblast culture has not been established, further analysis to obtain specific diagnosis is difficult; looking for parental heterozygosity for CPT II or a translocase defect has been tried, but remains a technical challenge (3).

### Genetic counseling

CACT deficiency is an autosomal recessive disorder of fatty acid oxidation with a severe phenotype. As soon as proof of a CACT defect in the index case or parental carrier status has been obtained, genetic counseling can be offered to the family.

### Antenatal diagnosis

CACT deficiency can be diagnosed prenatally using a biochemical approach to assess cultured foetal cells (trophoblasts or amniocytes) with *in vitro* fatty acid oxidation assays and/or the carnitine-acetylcarnitine exchange assay (4, 16). Alternatively, when the mutational status of the proband is known, chorionic villi may be directly

used for mutation analysis, providing an earlier diagnosis (24,25,30).

### Unsolved questions

The mechanism leading to hyperammonemia is not well known. One hypothesis is an urea cycle dysfunction due to defective N-acetyl-glutamate synthesis secondary to energy shortage and insufficient supply of mitochondrial acetylCoA. If so, administration of carbamyl-glutamate as a substitute for N-acetylglutamate needs to be evaluated as therapy to control the hyperammonemia.

Another hypothesis is that hyperammonemia might reflect the shortage of free carnitine since carnitine has been implicated in the transcription of urea-cycle enzymes (31).

The occurrence of neonatal hypocalcemia in CACT deficiency and mitochondrial trifunctional protein deficiency has not yet received a definite explanation: energy shortage has been considered responsible for hypothyroidism or myolysis.

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