Fatty Acid Oxidation Disorders

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[Primary Generalized Carnitine Deficiency (carnitine transport defect) 1](#_Toc119917359)

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Most are autosomal recessive.

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| **INFANTILE** |
| Medium-chain **acyl-CoA dehydrogenase** deficiency (MCAD) |
| Long-chain **acyl-CoA dehydrogenase** deficiency (LCAD) |
| Short-chain **acyl-CoA dehydrogenase** deficiency (SCAD) |
| CPT II deficiency (infantile form) |
| **CHILDHOOD** |
| Carnitine transport defect |
| CPT I deficiency |
| Long-chain L-3 hydroxyacyl-CoA dehydrogenase (LCHAD, trifunctional enzyme) |
| **ADULTHOOD** |
| CPT II deficiency (adult form) |

CPT - Carnitine Palmitoyl Transferase

Three main presentations:

1. acute toxic hepatic Reye-like **encephalopathy** + episodes of fasting **nonketotic** **hypoglycemia** in first 2 years of life (MCAD)
2. skeletal / cardiac **myopathies** with weakness + low plasma carnitine (carnitine deficiencies, CPT I and II deficiencies, LCAD, LCHAD, SCAD): see Met1 p.
   1. dynamic myopathy (dynamic exercise intolerance with myoglobinuria) - CPT I and II deficiencies
   2. static myopathy (static weakness with lipid storage myopathy) - carnitine deficiencies
3. nonketotic **hypoglycemia** + very low plasma carnitine + absent dicarboxylicaciduria (carnitine transport defect).

Carnitine Deficiency

1. Primary:
   1. primary generalized (systemic) carnitine deficiency
   2. primary muscle carnitine deficiency
2. Secondary

Primary Generalized Carnitine Deficiency (carnitine transport defect)

**High-affinity carnitine receptor defect** - carnitine fails to be taken up in muscle, heart, and kidney (but not liver):

1. kidney fails to conserve carnitine by reabsorption → **very low plasma [carnitine]** (<10 µM).\*
2. very low plasma [carnitine] → decreased passive diffusion into liver → impaired ketogenesis → **nonketotic** **hypoglycemia**
3. accumulating acyl-CoA becomes substrate for peroxisomal β-oxidation – this produces *medium-chain fatty acids* and *dicarboxylic acids*, which do not require carnitine for mitochondrial entry → **absent dicarboxylicaciduria**.\*

\* pathognomonic of carnitine transport defect.

Clinical Features

* rare disorder, unknown exact incidence.
* two major types:
  1. **early presentation** (3 months to 2½ years) - episodes of acute ***hepatic Reye-like encephalopathy***, ***nonketotic hypoglycemia*** accompanied by hyperammonemia and ALT & AST↑ after short fast (esp. if patient is being fed carnitine-free formula) → early death.
  2. **later presentation** (1 to 7 years):
     1. progressive ***cardiomyopathy*** → cardiac decompensation and respiratory distress.
     2. fixed lipid-storage ***myopathy***.

Diagnosis

- measuring ***carnitine uptake*** by fibroblasts and leukocytes (< 10% of control rates).

* very low plasma [carnitine].

Treatment

* **hypoglycemia**: intravenous *glucose* + long-term oral *L-carnitine* 100-120 mg/kg/day.
* **cardiomyopathy** → oral *L-carnitine* in higher doses (up to 175 mg/kg/day).

Primary Muscle Carnitine Deficiency

* diminished muscle uptake of carnitine.
* presents in childhood – progressive\*, painless ***limb-girdle myopathy*** (fixed lipid-storage myopathy). \*may end in death
* normal serum [carnitine]; serum CK↑.
* [carnitine]↓ in muscle biopsy tissue.

Treatment

* *carnitine* replacement in large doses has inconsistent benefit.
* some patients respond to *diet substituting* medium-chain for long-chain triglycerides, *riboflavin*, **prednisone**, **propranolol**.

Secondary Carnitine Deficiency

Etiology

1. enzymatic **β-oxidation defects** (e.g. acyl-CoA dehydrogenase deficiencies\*)

\* most commonly *medium-chain acyl-CoA dehydrogenase* deficiency (see below)

1. **mitochondrial** **dysfunction**
2. **insufficient intake** (parenteral nutrition)
3. **decreased synthesis** (cirrhosis)
4. **excessive loss** (renal disease, dialysis, Fanconi's syndrome, organic acidemia, diarrhea)
5. impaired metabolism of **valproic acid** (formed valproylcarnitine is lost in urine).
   * accumulating acyl-CoA molecules are converted to medium and long-chain acylcarnitines, which induce defect in tissue uptake of free carnitine.
   * *acylcarnitines* are more readily excreted in urine → negative carnitine balance.

Clinical Features

* most present in infancy or early childhood with ***Reye's syndrome-like episodes***.
* some surviving adults experience ***fixed lipid storage myopathy***.

Diagnosis

* muscle biopsy - lipid storage.
* [carnitine]↓, but [esterified carnitine] may be ↑ (esp. after oral supplementation of depleted carnitine stores).
* urinary acylcarnitines↑ - critical differentiation from primary carnitine deficiency!
  + different metabolic blocks in fatty acid metabolism lead to excretion of distinct urinary acylcarnitines - identify specific enzyme deficiencies.

Treatment

* *carnitine* supplementation produces variable results.
* some cases of multiple ***flavin-dependent dehydrogenase*** deficiency respond to *riboflavin*.

Medium-Chain Acyl-CoA Dehydrogenase Deficiency

- most common mitochondrial β-oxidation disorder (frequency 1 in 10,000-20,000).

Clinical Features

Phenotypical heterogeneity (present at age 3-15 months, rarely after 4 years):

1. **sudden infant death syndrome**

Risk of death with first episode ≈ 20%

Previous unexplained sibling deaths should raise MCADD as possible diagnosis!

1. recurrent **Reye's-like syndrome** (after fasting, prior viral respiratory or GI infection)
2. episodic **nonketotic hypoglycemic coma** with hyperammonemia, abnormal liver function tests.

Diagnosis

* serum [carnitine]↓
* urine [acylcarnitines]↑ with specific profile; also useful for *screening of siblings*.
* **enzyme assay** on cultured skin fibroblasts, muscle, liver, lymphocytes.
* **liver biopsy**:
* liver steatosis, which disappears on recovery.
* hepatic mitochondria show increased matrix density and intracristal widening, giving condensed appearance (vs. Reye's syndrome - matrix swelling and rarefaction).

Treatment

* 10% dextrose i/v.
* **avoid fasting** (frequent short feeds).
* *L-carnitine* 100 mg/kg/day orally.

Carnitine Palmitoyl Transferase Deficiency

CPT II deficiency

- long-chain acylcarnitines cannot be converted to acyl-CoAs.

* acylcarnitines accumulate in mitochondrial matrix and are transported out into plasma → may produce cardiac arrhythmias.
* plasma and tissue [carnitine]↓, long-chain acylcarnitines↑.
* dicarboxylicaciduria is absent (see carnitine transport defect).

Two presentations:

1. more common **adult form** – **dynamic myopathy** with myoglobinuria\* (most common cause of recurrent myoglobinuria; more common than glycogenoses!)

\*vs. carnitine deficiency – static myopathy

* + autosomal recessive (1p32).
  + affects males at age 15-30 years.
  + triggering factors (increase muscle dependence on free fatty acids) - prolonged exercise, cold, infections, fasting.

N.B. patients tolerate brief, intense exercise (vs. glycogenoses)

* + long-term muscle weakness is rare, although lipid storage may be seen.
  + 25% patients develop renal failure secondary to episodic myoglobinuria.
  + diagnosis - ***CPT activity assay in muscle***; muscle biopsy – normal (except after rhabdomyolysis episode).
  + treatment – frequent low-fat, high-carbohydrate meals.

1. fatal **infantile form**
   * **nonketotic hypoglycemic coma** without dicarboxylicaciduria
   * seizures, hepatomegaly, cardiomegaly, cardiac arrhythmia.

CPT I deficiency

* infancy / childhood - **Reye-like illness** with hypoketotic hypoglycemia, encephalopathy, hyperammonemia, and liver dysfunction.