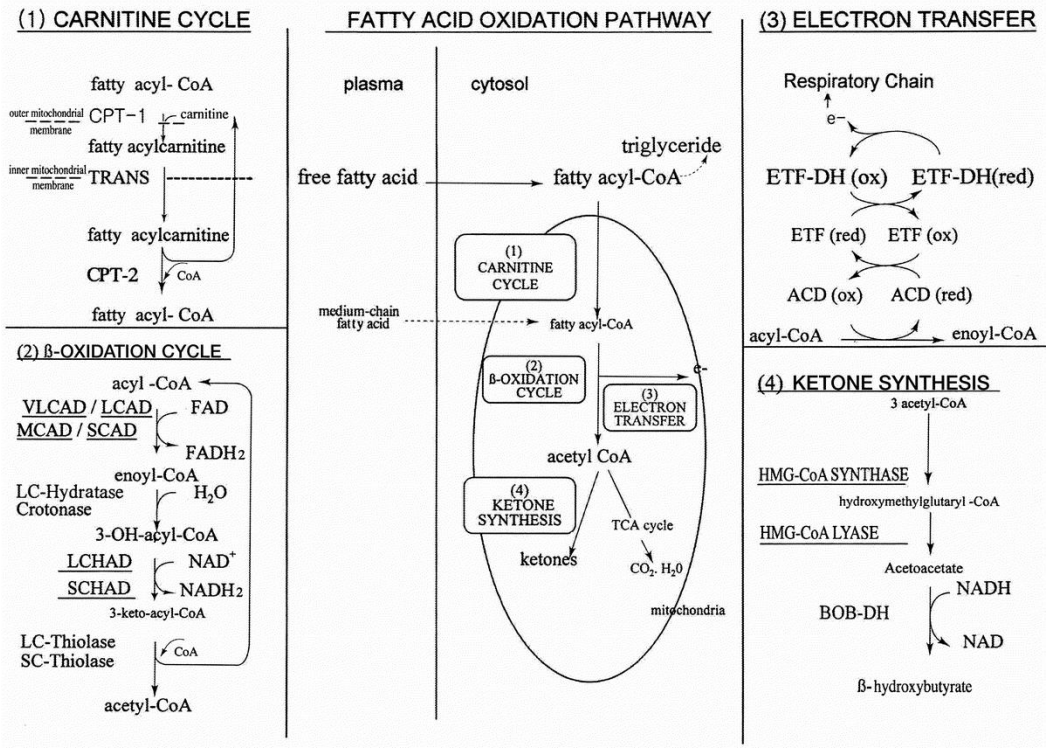
LONG TERM MANAGEMENT MEDIUM CHAIN ACYL CO-A DEHYDROGENASE DEFICIENCY MCAD

OMIM# 201450

Definition:

- Autosomal recessive disorder, one of the most common fatty acids oxidation defects.
- Caused by deficiency of Medium-chain acyl-coenzyme A dehydrogenase (MCAD)which is one of the enzymes involved in mitochondrial fatty acid β-oxidation, which fuels hepatic ketogenesis, a major source of energy once hepatic glycogen stores become depleted during prolonged fasting and periods of higher energy demands.
- It is prevalent in individuals of European (especially northern) descent. The overall frequency of the disorder has been estimated to range between 1:5000 and 1:20000; variability is related to the ethnic background of the population studied. (1-4)

Pathway:



Clinical Presentation:

- Usually present between ages 3- 24 months, although presentation in adulthood is also possible.
- Hypoketotic hypoglycemia, Reye syndrome, seizure and/or sudden death, provoked by prolonged fasting or catabolic stress during episodes of infection**.**
- Patients are asymptomatic in the interval between episodes of decompensation, but survivors of metabolic crisis may have severe neurological sequelae.
- Hepatomegaly is usually present during acute decompensation, which is also characterized by hypoketotic (not necessarily nonketotic) hypoglycemia, increased anion gap, hyperuricemia, elevated liver transaminases, and mild hyperammonemia.
- Maternal pregnancy complications such as HELLP syndrome (**h**emolysis, **e**levated **l**iver enzymes, **l**ow **p**latelets) and **a**cute **f**atty **l**iver of **p**regnancy (AFLP) may be more frequent (as for other fatty acid β-oxidation disorders) when the fetus has MCAD deficiency
- Mortality rate is 22% at the acute presentation before the diagnosis is made, and 21% develop disabilities after the diagnosis.(1-5)

Diagnosis:

- By newborn screening through acylcarnitines profile which showed high C_6, C_8, C_{10} carnitines and C8/C10 ratio and C8/C2 ratio
- Urine organic acids showed elevated medium-chain dicarboxylic acids with a characteristic pattern (C6>C8>C10), while ketones are inappropriately low. During acute episodes, 5-hydroxy hexanoic acid, hexanoylglycine, phenylpropionylglycine, and particularly suberylglycine are elevated too
- Diagnosis is confirmed by measurement of enzyme assay in WBC or cultured fibroblasts and DNA molecular testing of *ACADM* gene.(1-4)

Genetics:

- AR disorder
- The common mutation (c.985A>G) in the MCAD gene accounts for 80% of clinically ascertained cases.(1)

Treatment:

1. <u>Acute episode treatment guidelines (Emergency):</u>

- ABC (or now CAB).
- Insert an IV line and take blood for blood gases, chem 1, Ammonia (NH3), lactic acid & CBC, blood C/S (if patient febrile),liver transaminase, CK level and acylcarnitine profile.
- If hypoglycemic <3.5 give 3 ml/kg of D10
- If normoglycemic but patient cannot tolerate orally or if patient has diarrhoea, vomiting, dehydration, acidosis, high fever start 1 1/2 I.V.F as D10 1/2NS +KCl 20meq/l. Re-adjust according to lab results.
- Until the intravenous line is started, it is imperative to provide if possible / safe source of glucose like polycose solution
- Give carnitine 50mg/kg/dose IV then continue same dose divided q6.
- DO NOT administer lipids or acetylsalicylic acid

2. <u>Transition to long term management (Wards protocol):</u>

- Follow up with metabolic genetics dietitian.
- Continue on above measure until oral fluids are taken well and tolerated, and the patient is in normal mental status with normal glucose.
- Monitor glucose, chem1, acid base status and ammonia if high
- Titrate IVF according to PO intake until discontinue.
- Shift to oral carnitine 100mg/kg/day divided q6
- Discharge the patient if the following parameters achieved**:**
- Normal clinical status as home before crises**.**
- Normal plasma level ammonia achieved**.**
- Normal eletrolytes and no ketones in the urine**.**
- For new diagnosed case: parents educated about the disease natural history, formula, medications and sick day protocol**.**
- For new diagnosed case: Emergency card provided to the parents
- Family are comfortable with preparation of formula and sick day protocol
- Calculate the dosage of medications and ensure that had appropriate dosages / kg**.**
- Give appointment with General Metabolic Genetics Clinic 2 week after discharge with plasma aminoacids and electrolytes, prealbumin prior to appointment.

3. Long term management (home and outpatient visits)(1-3, 6)

- Avoidance of fasting with frequent feeding according to the age (see table 1)

Table1: Tolerance of fasting in MCAD deficiency:

Age (months)	Number of hours
Neonates	3
1-6	4
6-12	8
12-24	10
>24	12

- The aim of dietary management includes:
  - Normal weight gain, linear growth, and head growth.
  - Normal psychomotor development, as assessed by serial examinations and valid developmental screening tools (e.g., Denver Developmental Screening Test II).
- Many authors recommended the patient should be on high carbohydrates low fat diet(2, 3), however, the need for reduction of dietary fat to less than30% of total calories are controversial.(1)
- Toddlers could receive 2 g/kg of uncooked cornstarch as a source of complex carbohydrates at bedtime to ensure sufficient glucose supply overnight.
- Chronic carnitine supplementation or increase carnitine dose during stress is controversial(1). However, many authors recommended to treat the patients with 100mg/kg/day to prevent secondary canitine deficiency.(3)

4. Monitoring:

	At diagnosis	3 months	6 months	1 year	Yearly thereafter
Acylcarnitine profile (for free carnitine measurement)	+	+	+	+	+
Clinic and dietitian visit	+	+	+	+	+

5. Sick day management:

- Parents are advised to make a sick day formula by adding 1 tsp polycose to 100 mL infant formula or 1 Tbsp Polycose to 120 mL juices during illness and feed every two hours.
- If patient refuses sick day formula, vomits or deteriorates despite changing to a sick day formula, then, the patient should go to ER.

6. Management with surgical procedure:

- Ensure that the patient on his usual state of health prior to procedure.
- CBC, diff, blood sugar, electrolytes, pH, anion gap, lactate, liver enzymes, PT, PTT one day prior to procedure.
- Start IVF D10 as soon as NPO start at 11/2 maintenance +kcl20meq/l (adjusted according to chem1 result)

References:

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