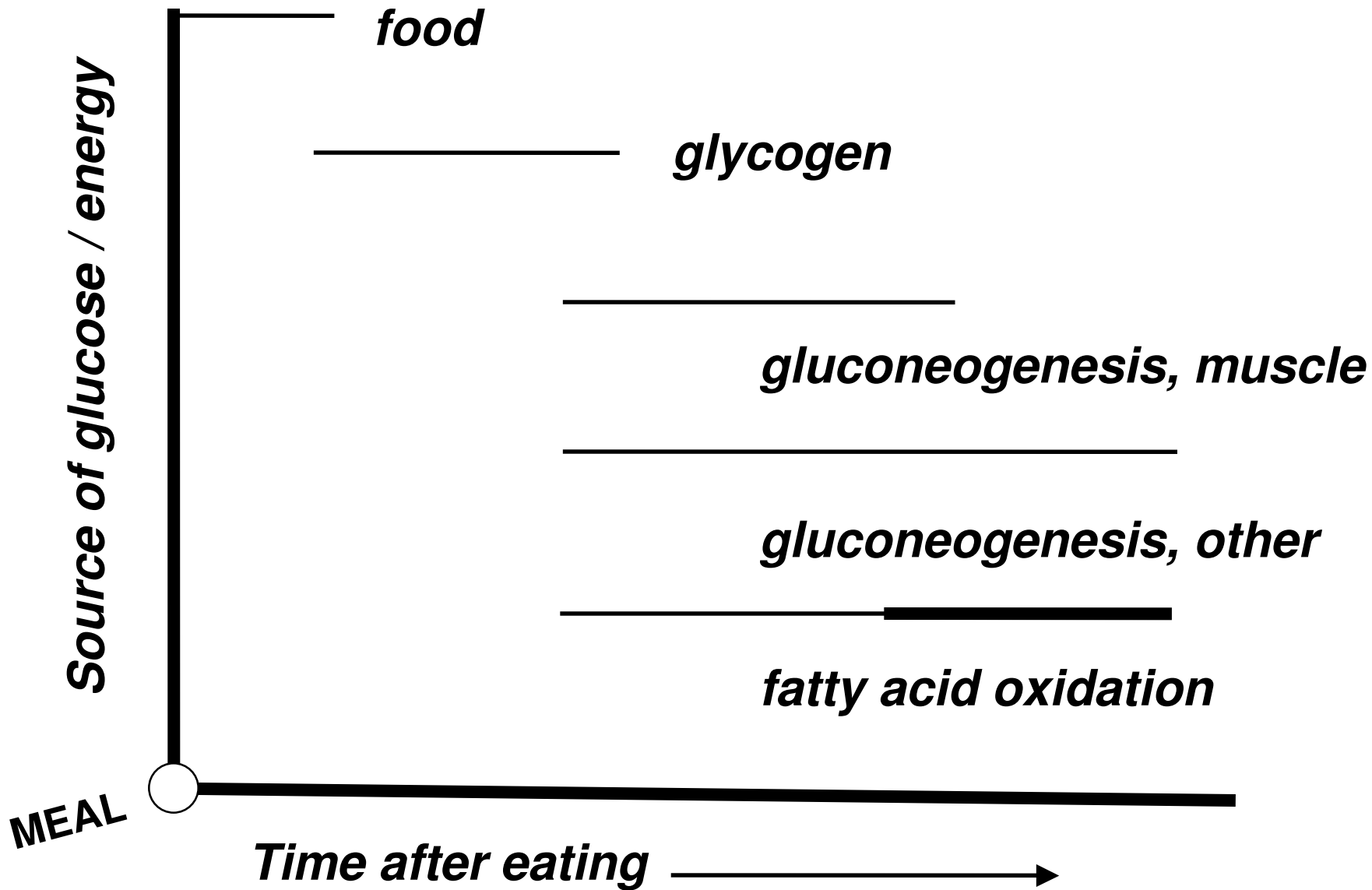


**FATTY ACID OXIDATION
DEFECTS:
*Adult Presentations***

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SYMPTOM TRIGGERS

- When eating well, and while otherwise healthy (and anabolic), patients may show no symptoms.
- Exercise or sickness, or prolonged fasting...
...when food intake is inadequate and calorie intake cannot keep up with demand, symptoms may occur.

PRESENTATION IN ADULTS

- Nausea and vomiting
- Encephalopathy – lethargy, coma, seizures
- Easy fatigability, muscle weakness
- Liver enlargement, dysfunction
- Cardiac muscle dysfunction
- Muscle pain and myoglobinuria
- Reye syndrome-like illness

Reye Syndrome:

Metabolic Differential Diagnosis

- Fatty acid oxidation defects
- Disorders of carnitine transport, metabolism
- Urea cycle disorders
- Organic acidemias
- Disorders of pyruvate metabolism, oxidative phosphorylation
- Defects in carbohydrate metabolism
(hereditary fructose intolerance, disorder of gluconeogenesis)

**Long chain fatty acid oxidation
disorder –**

**MEDIUM CHAIN ACYL CoA
OXIDASE (MCAD)
DEFICIENCY**

FATTY ACID OXIDATION DISORDERS

Incidence

- Estimated at 1/10,000-1/14,000 live births (newborn screening results)
- Accounts for ~5% of sudden infant death syndrome (SIDS) (*Boles et al, 1998*)

MCAD: Sudden and Unexpected Death of a 45-year-old Woman

(Raymond K et al, 1999)

The patient was previously well, taking no medications. She was hospitalized for distal colectomy for biopsy-proven adenocarcinoma. Physical examination was normal at the time of surgery.

In retrospect, she complained of nausea and discomfort while fasting overnight in preparation for a colonoscopy.

MCAD: Sudden and Unexpected Death of a 45-year-old Woman

Pre-operatively, glucose measured 91 mg/dL. AST and ALT were normal.

The resection was tolerated well.

The liver looked normal by direct examination.

The patient was kept NPO and provided 2 liters/day of Lactated Ringer's (glucose-free) for 2 days.

MCAD: Sudden and Unexpected Death of a 45-year-old Woman

On the morning of the 3rd post-op day, she complained of nausea and drowsiness.

- Blood glucose=68 mg/dL
- AST=147 U/L (NL=70-110)

Her mental status deteriorated; she was unconscious by early afternoon.

CT scan negative.

The patient died following a respiratory arrest that day.

MCAD: Sudden and Unexpected Death of a 45-year-old Woman

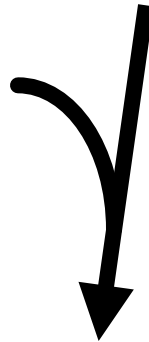
Post-mortem examination was significant for the prominent yellow fatty appearance of the liver and kidneys.

Histology showed diffuse macrovesicular and microvesicular fatty infiltration.

ORGANIC ACYL-CoA

FATTY ACYL-CoA

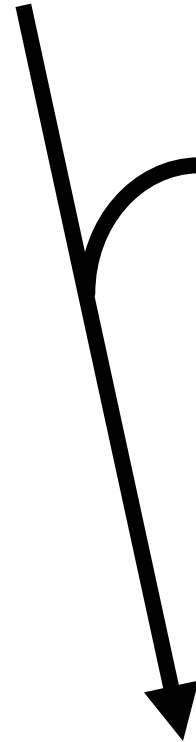
CARNITINE



ORGANIC ACYLCARNITINE

FATTY ACYLCARNITINE

GLYCINE



ORGANIC ACYLGLYCINE

FATTY ACYLGLYCINE

MCAD: Sudden and Unexpected Death of a 45-year-old Woman

Acylcarnitine profile showed marked elevations of medium chain fatty acid species – C6, C8 and C10:1.

Free fatty acid profile confirmed the elevations of C8, C10, and C10:1

DNA testing on liver tissue identified homozygosity for the common, deleterious MCAD deficiency mutation – A985G.

MCAD: Sudden and Unexpected Death of a 45-year-old Woman

- ✓ The patient had MCAD deficiency.
- ✓ The patient was sick but not hypoglycemic.
- ✓ Fatty acid oxidation defects are not just “childhood diseases”.
- ✓ Patients should not be thought of as asymptomatic but as ***presymptomatic***.

ENCEPHALOPATHY:

Causes

- Fatty acid oxidation disorders are disorders of energy metabolism in which the brain “runs out of energy”:
 - glucose stores are exhausted;
 - ketone production is diminished;
 - gluconeogenesis is impaired.
- The accumulating metabolites are toxic to the brain, causing brain swelling and coma.

VLCAD: Young Woman with Persistent Hypoglycemia, Rhabdomyolysis, and Coma

(Kluge, S et al, 2003)

The 32 year old woman had a history of myopathy of unknown cause with muscle weakness, pain, and recurrent elevations of CPK. An extensive myopathy work-up was negative.

A 17 year old brother had died of Reye syndrome.

VLCAD: Young Woman with Persistent Hypoglycemia, Rhabdomyolysis, and Coma

The patient was unconscious with dilated pupils, tachycardia, hypotension (70/40), and hypothermia (33.6 °C)

- Blood gases: pH=7.06, pCO₂=52, HCO₃=14
- Blood glucose=31 mg/dL
- CK=6047 U/L
- Urine negative for ketones

VLCAD: Young Woman with Persistent Hypoglycemia, Rhabdomyolysis, and Coma

An echocardiogram showed reduced left ventricular dysfunction, ejection fraction=10%.

The patient required large amounts of glucose to prevent hypoglycemia, and received bicarbonate, epinephrine, calcium, and fluids.

Chest x-ray showed bilateral infiltrates consistent with pneumonia.

VLCAD: Young Woman with Persistent Hypoglycemia, Rhabdomyolysis, and Coma

The patient remained comatose with dilated, non-responsive pupils, and absent deep tendon reflexes.

The CK steadily rose to 65,000.

The following day, dialysis was begun for renal failure.

VLCAD: Young Woman with Persistent Hypoglycemia, Rhabdomyolysis, and Coma

Ultrasound of the liver showed severe steatosis.

Liver biopsy confirmed severe micro- and macro-vesicular steatosis, “affecting >80% of hepatocytes.”

VLCAD: Young Woman with Persistent Hypoglycemia, Rhabdomyolysis, and Coma

The patient ultimately responded to treatment with a slow recovery.

She was transferred from the ICU after 20 days, and discharged home in good condition after 13 weeks.

VLCAD: Young Woman with Persistent Hypoglycemia, Rhabdomyolysis, and Coma

Acylcarnitine analysis showed a marked elevation in long chain fatty acid species – C14, C14:1, C14:2.

Urine organic acids showed the abnormal excretion of dicarboxylic acids suggesting impairment of fatty acid β -oxidation.

Fibroblast testing showed oxidation of palmitate (C16); enzyme testing confirmed VLCAD deficiency.

**Skeletal and cardiac muscle
utilize sugar *AND FAT* as primary
energy sources.**

Maternal Acute Fatty Liver of Pregnancy with Fetal Trifunctional Protein Deficiency

(Isaacs JD et al, 1996)

This otherwise healthy 43 year old woman had had two previous uncomplicated term pregnancies.

She presented at 35 weeks gestation with nausea, vomiting, fatigue, and malaise. She had no edema.

Maternal Acute Fatty Liver of Pregnancy with Fetal Trifunctional Protein Deficiency

- AST=293 (NL=14-43)
- Total bilirubin=5.0 (NL=0-1.3)
- Prothrombin time=15.3 sec (NL=11.4-13.3)
- Fibrinogen=164 (NL=300-600)
- Platelets=75,000 (NL=140,000-350,000)
- Hepatitis serologies were all negative.

An abdominal ultrasound was consistent with diffuse hepatic steatosis.

Maternal Acute Fatty Liver of Pregnancy with Fetal Trifunctional Protein Deficiency

A 35-week male infant was delivered by emergency cesarean section for fetal distress.

The mother developed modest postoperative bleeding but recovered. All biochemical abnormalities resolved.

Maternal Acute Fatty Liver of Pregnancy with Fetal Trifunctional Protein Deficiency

At four months of age, the infant developed lethargy, coma, hypoglycemia, and metabolic acidosis. Diagnostic testing revealed trifunctional protein deficiency.

FAOD / CARNITINE DISORDERS ASSOCIATED WITH LIVER DISEASE DURING PREGNANCY

- Defects in carnitine metabolism/transport:
 - Carnitine palmitoyltransferase (CPT) I def'y
- Defects in fatty acid β -oxidation –
 - Long chain hydroxyacyl CoA dehydrogenase (LCHAD) deficiency
 - Medium chain CoA dehydrogenase (MCAD) def'y
 - Short chain CoA dehydrogenase (SCAD) def'y

MATERNAL LIVER DISEASE

- **HELLP** syndrome (**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets)
 - 0.1-1% of deliveries
 - 4-12% of women with severe pre-eclampsia
- **AFLP** (**A**cute **F**atty **L**iver of **P**regnancy)
 - 1/1,000-1/15,000 deliveries

ACUTE FATTY LIVER OF PREGNANCY

- Usually occurs in the third trimester
- Abdominal pain, nausea, vomiting
- Hepatic failure
- Coma
- Hypoglycemia, hyperammonemia
- Renal failure
- Coagulopathy and hemorrhage

LCHAD Deficiency

- Fetal LCHAD deficiency in women with AFLP ~ 20%
- Fetal LCHAD deficiency in women with HELLP syndrome < 1-2%
- During an LCHAD-affected pregnancy, ~50% chance of maternal liver disease:
 - 30% HELLP
 - 30% AFLP
 - Remainder – pre-eclampsia, maternal cholestasis

Maternal liver disease correlates with the presence of common LCHAD-deficiency mutation (G1528C) mutation in the fetus.

ACUTE FATTY LIVER OF PREGNANCY

Pathogenesis in LCHAD carriers

- Increased triglycerides, free fatty acids, most marked at term.
- In pre-eclampsia, FFA levels even higher.
- Peripheral lipoprotein lipase partially inhibited.
- Fatty acid oxidation reduced by 26-40% in mice.

ACUTE FATTY LIVER OF PREGNANCY

Pathogenesis in LCHAD carriers

- Transfer of hepatotoxic long chain fatty acid metabolites from fetus to mother; linked to liver damage in AFLP.

RECOMMENDATIONS:

History

– Any patient with suggestive symptoms, especially if associated with fasting or poor intake, or exercise –

- Fasting intolerance
- History of liver or muscle disease
- Family history (liver or muscle disease, Reye syndrome)

RECOMMENDATIONS:

Testing

– Any patient with suggestive symptoms, especially if associated with fasting or poor intake, or exercise –

- Blood glucose, ammonia
- Blood acylcarnitines
- Urinalysis (ketones)
- Urine organic acids
- Urine acylglycines

RECOMMENDATIONS:

Testing

– In pregnancies complicated by AFLP -

- Molecular screening (G1528C)
- If positive, test the spouse and all children.
- Treat infants at risk as if they have a fatty acid oxidation defect until a diagnosis is made or ruled out.

RECOMMENDATIONS:

Treatment

– *Any patient with a fatty acid oxidation defect:*

- Avoid prolonged fasting (greater than a regular overnight fast).
- If cannot tolerate the required calorie intake, provide IV fluids with dextrose.
- ?fat restriction; however, if the patient is sick and/or not eating, push carbohydrates and limit fats.

RECOMMENDATIONS:

Treatment

- *Any patient with a fatty acid oxidation defect:*
- Provide 10% dextrose with normal saline at 1.25x maintenance rate.