ANATOMY OF A METABOLIC CRISIS: FAOD-style

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NORMAL PHYSIOLOGY

**Anabolic** –

- Eating well
- Calories eaten > body’s needs

<table>
<thead>
<tr>
<th>BRAIN</th>
<th>MUSCLE</th>
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<tbody>
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</tr>
<tr>
<td></td>
<td>FAT</td>
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NORMAL PHYSIOLOGY

**Catabolic –**

- Not eating well; fasting
- Body’s needs > calories eaten

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Source of glucose / energy

- food

- glycogen

- gluconeogenesis, muscle

- gluconeogenesis, other

- fatty acid oxidation

Time after eating

MEAL
NORMAL PHYSIOLOGY

**Catabolic** –

- Not eating well; fasting
- Body’s needs > calories eaten

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<td>(as ketones)</td>
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NORMAL PHYSIOLOGY

Exercise –

MUSCLE
uses
GLUCOSE
↓
FAT (aerobic)
FAT DEPOSITS

↓

fatty acids

↓

LIVER
LONG CHAIN FATTY ACYL CoA

CARNITINE

Mitochondrial Membrane

CARNITINE

LONG CHAIN FATTY ACYL CoA
Mitochondrial Membrane

LONG CHAIN FATTY ACYL CoA

LONG CHAIN β-OXIDATION ENZYMES
Mitochondrial Membrane

LONG CHAIN FATTY ACYL CoA

ACETYL CoA

KETONE BODY
Mitochondrial Membrane

MEDIUM CHAIN FATTY ACYL CoA

MEDIUM CHAIN β-OXIDATION ENZYMES
Mitochondrial Membrane

MEDIUM CHAIN FATTY ACYL CoA

ACETYL CoA

KETONE BODY
SHORT CHAIN FATTY ACYL CoA

Mitochondrial Membrane

SHORT CHAIN β-OXIDATION ENZYMES
SHORT CHAIN FATTY ACYL CoA

ACETYL CoA

KETONE BODY
NORMAL PHYSIOLOGY

LIVER

FAT

ACETYL CoA

KETONES

BRAIN

ENERGY

ACETYL CoA

KETONES

BLOOD
MEET EC, with MCAD deficiency

• Patient EC started sleeping through the night at 4-5 months of age.
• At 13 months, she developed her first episode of lethargy. Parents had difficulty waking her up in the morning. In the ER, viral infection.
• She had eight episodes of early morning lethargy between 13 and 20 months of age.
EC, with MCAD deficiency

- The episodes usually occurred in the morning - if she missed her bed-time snack, or if she had an infection. She went limp and/or stared without responding. Her temperature could drop to 94-95°F. This would last for 4-6 hours. Then she “returned to normal”, recovering after drinking juice.
EC, with MCAD deficiency

• EC’s development was appropriate.
• She was evaluated by Neurology for the possibility of seizures; an EEG was normal.
EC, with MCAD deficiency

- On one occasion, EC found lethargic, and brought to the ER:
  - **Glucose = 36 mg/dL (LOW)**
  - Insulin = 0.2 IU/mL (LOW)
  - Cortisol = 21.9 µg/dL (HIGH)
  - Free fatty acids = 2.66 mEq/dL (HIGH)
  - **β-hydroxybutyrate = 0.3 mmol/L (LOW)**
Source of glucose / energy

Time after eating

MEAL

gluconeogenesis, other

fatty acid oxidation
COMPONENTS OF EC’s CRISIS

LOW ENERGY
COMPONENTS OF EC’s CRISIS

BUT patients can be very sick

AND NOT BE HYPOGLYCEMIC
Free Fatty Acids, Ketones, mM

Hours of Fasting

Glucose, mg/dL

MCAD Deficiency

(Semykina et al, 2000)

SYMPTOM ONSET

Free Fatty Acids

Ketones

Glucose

8 12 16 20 24 28 32

80 60 40 20 0

0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0

20 40 60 80 100

0 1 2 3 4
ACYLCARNITINES in MCAD deficiency

• C6 - hexanoic acid $\rightarrow$ hexanoylcarnitine
• C8 – octanoic acid $\rightarrow$ octanoylcarnitine
• C10 – decanoic acid $\rightarrow$ decanoylcarnitine
ACYLCARNITINES in MCAD deficiency

• Long and medium chain fat can be toxic to brain cells $\rightarrow$ coma

• Fatty acids, acylcarnitines and the lack of CoA disrupt enzymes involved in glucose production, and energy production pathways

• Evidence of severe energy stress in the brain (oxidative damage)
COMPONENTS OF EC’s CRISIS

TOXICITY
ACYLCARNITINES in MCAD deficiency

- C6 - hexanoic acid → hexanoylcarnitine
- C8 – octanoic acid → octanoylcarnitine
- C10 – decanoic acid → decanoylcarnitine

These can interfere with the metabolism of ammonia
AMMONIA

• Toxic to the brain
• Accumulation causes brain swelling
COMPONENTS OF EC’s CRISIS

TOXICITY
FAT DEPOSITS

↓

fatty acids

↓

LIVER
ALSO – LIVER DISEASE

- Acylcarnitines interrupt the metabolism of fat
- Liver dysfunction – high liver enzymes
- Acute fatty liver
COMPONENTS OF EC’s CRISIS

TOXICITY
LOW CARNITINE

• Reduced ability to bind the toxic intermediate compounds and facilitate their excretion

• Reduced ability to liberate CoA for other important reactions

• Its degree of importance remains controversial
Mitochondrial Membrane

SHORT/MEDIUM CHAIN FATTY ACYL CoA

NEW KETONE BODIES

SHORT, MEDIUM CHAIN DEFECT → MANY KETONE BODIES

HAPPY MUSCLES
Mitochondrial Membrane

LONG CHAIN FATTY ACYL CoA

NEW KETONE BODY

LONG CHAIN OXIDATION DEFECT → FEW KETONE BODIES

ANGRY MUSCLES
MUSCLE DISEASE

- In long chain fatty acid oxidation defects
- Skeletal muscle –
  - muscle pain, weakness
  - muscle damage (rhabdomyolysis) \(\rightarrow\) spilling into the urine (myoglobinuria)
  - severe myoglobinuria can cause acute kidney failure and heart rhythm problems
- Cardiac muscle –
  - Cardiomyopathy \(\rightarrow\) heart failure
LONG CHAIN FAO CRISIS

LOW ENERGY
LONG CHAIN FAO CRISIS

TOXICITY
DIAGNOSIS
NEWBORN SCREENING IN MASSACHUSETTS (2012)

AMINO ACID DISORDERS
- PKU
- Maple syrup urine disease
- Biotinidase deficiency
- Propionic acidemia
- Methionine adenosyltransferase (s)
- Isovaleric aciduria
- Argininosuccinic aciduria
- Arginase deficiency
- Galactosemia

ORGANIC ACID DISORDERS
- MCAD deficiency
- OTC deficiency
- β-ketothiolase deficiency
- Glutaric acidemia I

FATTY ACID OXIDATION DEFECTS
- Primary screen

OTHER DISORDERS:
- Congenital hypothyroidism
- Congenital adrenal hyperplasia
- Congenital toxoplasmosis
- Hemoglobinopathies
- Cystic fibrosis
DIAGNOSIS CONFIRMATION

• DNA testing
• Enzyme or FAO function studies (usually from skin cells/fibroblasts)
MANAGEMENT
MANAGEMENT

PROVIDE ENERGY AS GLUCOSE
Why 10% Dextrose When Sick?

• “Catabolism” occurs when the amount of dietary or IV glucose falls below the basal glucose production rate in liver.

• Bier et al, 1977, determined this rate:
  \[ y = 0.0014x^3 - 0.214x^2 + 10.411x - 9.084 \]
  \( y = \) glucose production rate (mg/min)
  \( x = \) body weight (kg)
Example: 10 kg child

- $y=0.0014 \, x^3 - 0.214 \, x^2 + 10.411 \, x - 9.084$
  $y=$glucose production rate (mg/min)
  $x=$body weight (kg)

- Basal glucose production rate = 75.03 mg/min of glucose (or 7.5 mg/kg/min)

- 10% dextrose at maintenance provides 70 mg/min (or 7.0 mg/kg/min)

- 10% dextrose at 1.25x maintenance provides 87 mg/min (or 8.7 mg/kg/min)
PROVIDING GLUCOSE

• Provides energy:
  – to all organs

• Suppresses catabolism:
  – production of the toxic compounds
  – reduces production of ammonia
  – clears the fat accumulation in the liver and the liver dysfunction
  – helps limit muscle damage
MEDIUM CHAIN FAT IN LONG CHAIN FAO

- Bypasses the enzyme block and enables fat to be used as a source of energy
PROVIDE CARNITINE