Mitochondrial Dysfunction in the Organic Acidemias:

Mark S. Korson, MD
VMP Genetics
A case of methylmalonic acidemia

A 22 year old woman delivers a male at 37 weeks gestation following an unremarkable pregnancy, labor, and delivery. The baby was alert upon delivery. Weight measured 6-1/2 lb. Breast-fed well on day 1, then circumcised; afterwards, felt cold. By day 2, began to feed poorly, became hypoglycemic, transferred to the nursery. IV glucose given. Blood pH=7.27. Electrolytes showed a bicarbonate of 7, repeat 5. Intubated for transport, and given IV bicarbonate.
Upon arrival in the NICU, poorly responsive, jaundiced, with a deep labored breathing.

Labs:
- Bicarbonate 8, anion gap 32
- BUN 41, creatinine 1.9
- Ammonia 96 µmol/L (NL<95), repeat 212
- Urine ketones positive (3+)
The baby underwent dialysis. After placement of dialysis lines, repeat ammonia measured 1480 µmol/L. After two cycles - ammonia 586.

Urine organic acids - marked elevation of methylmalonic acid

*Diagnosis* - methylmalonic acidemia
ILE VAL MET THR

PROPIONYL CoA

PROPYIONYL CoA CARBOXYLASE

METHYLMALONYL CoA

SUCCINYL CoA

KREBS CYCLE

PROPIONATE FROM GUT BACTERIA

CHOLESTEROL SIDE CHAINS

ODD CHAIN FATS

FROM GUT BACTERIA
CHOLESTEROL SIDE CHAINS

ILE VAL MET THR

PROPIONYL CoA

CHOLESTEROL SIDE CHAINS
ODD CHAIN FATS

METHYLMALONYL CoA MUTASE

METHYLMALONYL CoA

SUCCINYL CoA

KREBS CYCLE

PROPIONATE FROM GUT BACTERIA

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Normal urine organic acid profile (GC/MS TIC)

(GC/MS TIC analysis)
Urine organic acids (propionic acidemia)

Propionate precursors

Lab session 1
Urine organic acids (propionic acidemia)

LEGEND:
1. lactic acid
2. 3-hydroxypropionic acid
3. 3-hydroxybutyric acid
4. 2-methyl-3-hydroxybutyric acid
5. acetoacetic acid (peak I)
6. 3-hydroxyvaleric acid
7. methylmalonic acid
8. 3-hydroxyisovaleric acid
9. acetoacetic acid (peak II)
10. ethylmalonic acid
11. isobutyrylglycine (di-TMS)
12. glutaric acid
13. 2-methylbutyrylglycine (di-TMS)
14. propionylglycine (di-TMS)
15. 3-methylglutaconic acid (peak I)
16. 3-methylglutaconic acid (peak II)
17. 3-hydroxyadipic lactone
18. isovalerylglucose (di-TMS)
19. isovalerylglucose (mono-TMS)
20. adipic acid
21. tiglylglycine (di-TMS)
22. tiglylglycine (mono-TMS)
23. 3-hydroxyglutaric acid
24. octenedioic acid
25. 3-hydroxyadipic acid
26. suberic acid
27. methylicolic acid (peak I)
28. methylicolic acid (peak II)
29. decenedioic acid (multiple isomers)
30. 3-hydroxyoctenedioic acid
31. 3-hydroxysuberic acid
32. sebacic acid
33. 3-hydroxydecalenoic acid
34. 3-hydroxysebacic acid
35. 3-hydroxydodecenoic acid (C12:2)
36. 3-hydroxyoctenedioic acid
37. 3-hydroxydodecanedioic acid
38. 3-hydroxytetradecanoic acid (C14:2)
39. 3-hydroxytetradecenoic acid
40. 3-hydroxytetradecanedioic acid

Ketones

Lab session 1
CHOLESTEROL SIDE CHAINS

ODD CHAIN FATS

CHOLESTEROL FROM GUT BACTERIA

ILE VAL MET THR

PROPIONATE

PROPIONYL CoA

KREBS CYCLE

SUCCINYL CoA

ACETYL CoA

OXALO-ACETATE

GLYCINE

CARNITINE

PROPIONYL-CARNITINE

PROPIONYL-GLYCINE

METHYLCITRATE

3-OH-PROPIONATE

3-OH-ISOVALERATE

METHYLCITRATE

PROPIONYL-GLYCINE

3-OH-PROPIONATE

ODD CHAIN FATS
Urine organic acids (propionic acidemia)

Lab session 1

Propionate metabolites
CHOLESTEROL SIDE CHAINS

ILE  VAL  MET  THR

PROPIONYL CoA

METHYLMALONYL CoA

METHYLMALONYL CoA MUTASE

SUCCINYL CoA

KREBS CYCLE

PROPIONATE FROM GUT BACTERIA

CHOLESTEROL SIDE CHAINS

ODD CHAIN FATS

ILE

VAL

MET

THR

PROPIONYL CoA

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KREBS CYCLE
Urine organic acids (methylmalonic acidemia)

Lab session 1
CHOLESTEROL SIDE CHAINS

ILE VAL MET THR

PROPIONYL CoA

METHYLMALONYL CoA

Succinyl CoA

KREBS CYCLE

HIGH BLOOD ACID LEVEL

LOTS OF KETONES

LOW WBCs LOW PLATELETS

HIGH AMMONIA

CHOLESTEROL ODD CHAIN FATS
METABOLIC CRISIS

Possible symptoms

Poor feeding, vomiting → dehydration
Lethargy, altered consciousness → coma
Looks “septic”
Rapid breathing
  • Metabolic acidosis
  • High ammonia
ACUTE COMPLICATIONS

Advanced crisis symptoms

Apnea
Slowing heart rate
Seizures
Hypothermia
Generalized/non-specific organ dysfunction
Stroke-like episode
Sudden death
LATE-ONSET PRESENTATIONS

Chronic symptoms

- Anorexia, vomiting
- Failure to thrive
- Protein intolerance
- Developmental delays/regression
- Hypotonia
- Dystonia/movement disorders
- Skin rash (Candida)
- Cardiomyopathy
CHRONIC COMPLICATIONS I

Long term

Growth retardation
Developmental delays, seizures
Dystonia/movement disorders
Basal ganglia stroke
METHYLMALONIC ACIDEMIA

BASAL GANGLIA

THALAMUS

METHYLMALONIC ACIDEMIA
METHYLMALONIC ACIDEMIA

BASAL GANGLIA:
- Caudate
- Putamen
- Globus pallidus

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CHRONIC COMPLICATIONS I

Long term

Growth retardation
Developmental delays, seizures
Dystonia/movement disorders
Basal ganglia stroke
Kidney failure
Pancreatitis
CASE - Propionic acidemia

“Casey” presented in the neonatal period. Had problems with global developmental delays, autistic features, hypotonia, seizures. Fed mostly by gastrostomy. Developed progressive retinal disease at age 18 years, died of acute cardiac decompensation at age 20 years.
CASE - Propionic acidemia

“Iris” presented in the neonatal period. Had problems with global developmental delays, hypotonia, seizures. Fed mostly by gastrostomy. Cardiomyopathy identified at age 16 years, progressive → died from cardiac failure at age 21
CHRONIC COMPLICATIONS II

Long term

Cardiomyopathy
Optic nerve atrophy $\rightarrow$ blindness
Hearing loss (sensorineural)
Diabetes
## PATHOGENESIS OF ORGANIC ACIDEMIAS

<table>
<thead>
<tr>
<th>Components</th>
<th>High acid / high ammonia / low glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Toxic accumulation(s)</td>
</tr>
<tr>
<td></td>
<td>Significant deficiency(ies)</td>
</tr>
<tr>
<td><strong>Overall energy deficiency</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impact from the triggering event (infection)</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic worsening</td>
</tr>
</tbody>
</table>

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ANY DEFECT IN ENERGY METABOLISM WITHIN THE MITOCHONDRIUM = MITOCHONDRIAL DISORDER
Respiratory chain
Complex V: ATP synthase

Oster G and Wang H. BBA 2000;1458:482
100s of MITOCHONDRIAL DISEASES

Characteristics
Multi-systemic
Onset at any age
Progressive
<table>
<thead>
<tr>
<th>Neurologic</th>
<th>Developmental delays</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Developmental regression</td>
</tr>
<tr>
<td></td>
<td>Hypotonia</td>
</tr>
<tr>
<td></td>
<td>Dystonia/movement disorders</td>
</tr>
<tr>
<td></td>
<td>Ataxia (unsteadiness)</td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
</tr>
<tr>
<td></td>
<td>Stroke-like episodes</td>
</tr>
</tbody>
</table>
METHYLMALONIC ACIDEMLIA

MITOCHONDRIAL DISEASE
Leigh variant
METHYLMALONIC ACIDEMIA

MITOCHONDRIAL DISEASE
Leigh variant

Isikay, Ped Neuro, 2014
PROPIONIC ACIDEMIA

MITOCHONDRIAL DISEASE
Leigh variant

Johnson, Ped Neuro, 2009
MITOCHONDRIAL DISEASE - SYMPTOMS/SIGNS

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Pain, cramping</td>
</tr>
<tr>
<td></td>
<td>Muscle injury</td>
</tr>
<tr>
<td>Hearing</td>
<td>Neurosensory impairment</td>
</tr>
</tbody>
</table>
MITOCHONDRIAL DISEASE - SYMPTOMS/SIGNS

Eyes/vision

- Blurriness, double vision
- Ptosis (droopy eyelids)
- Problems with night vision
- Retinal pigmentation, optic atrophy
MITOCHONDRIAL DISEASE - SYMPTOMS/SIGNS

Heart

Cardiomyopathy

Arrhythmia (heart rhythm problems)
| Kidney | Tubular dysfunction (problems with reabsorption) |
MITOCHONDRIAL DISEASE - SYMPTOMS/SIGNS

Gut

Dysmotility:

• Uncoordinated swallowing
• GE reflux, sticking, vomiting
• Gastroparesis with pain, distention, early satiety or anorexia
• Pseudo-obstruction
• Constipation
| Bladder | Neurogenic bladder with weakness and loss of control |
### MITOCHONDRIAL DISEASE - SYMPTOMS/SIGNS

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypothyroidism (low thyroid)</td>
</tr>
<tr>
<td></td>
<td>Adrenal dysfunction (low adrenal)</td>
</tr>
<tr>
<td></td>
<td>Parathyroid dysfunction (low parathyroid)</td>
</tr>
</tbody>
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100s of MITOCHONDRIAL DISEASES

<table>
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<th>Characteristics</th>
<th>Multi-systemic</th>
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<tr>
<td>Onset at any age</td>
<td>Progressive</td>
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<tr>
<td>Some symptoms can vary in intensity, like fatigue</td>
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</tr>
<tr>
<td>Weakness</td>
<td>When tested, muscles are weak</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------------</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Muscle strength varies over the day</td>
</tr>
<tr>
<td></td>
<td>After resting, patients may have normal strength</td>
</tr>
<tr>
<td></td>
<td>After exercise, patients may be weak, but can recover with rest</td>
</tr>
<tr>
<td></td>
<td>“Like a battery that discharges too rapidly”</td>
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</table>
100s of MITOCHONDRIAL DISEASES

Characteristics

Multi-systemic
Onset at any age
Progressive
Some symptoms can vary in intensity, like fatigue
Infections → long recovery time; if very prolonged, recovery may not be complete
Autonomic dysfunction
AUTONOMIC FUNCTIONS

- Heart Rate
- Temperature
- Sphincter control
- Skin color
- Blood pressure
- Sweating
- Gastrointestinal function
AUTONOMIC DYSREGULATION

- Fast or slow heart rate
- Temperature
- Sweating
- Gut & bladder function
- Skin color
- Blood pressure
AUTONOMIC FUNCTIONS

- Fast or Slow Heart Rate
- SWEATING
- SKIN COLOR
- BLOOD PRESSURE
- GUT & BLADDER FUNCTION
- TEMPERATURE
AUTONOMIC DYSREGULATION

- FAST OR SLOW HEART RATE
- SWEATING
- SKIN COLOR
- BLOOD PRESSURE
- HIGH / LOW / UNSTABLE TEMP
- GUT & BLADDER FUNCTION
AUTONOMIC FUNCTIONS

- FAST OR SLOW HEART RATE
- HIGH / LOW / UNSTABLE TEMP
- GUT & BLADDER FUNCTION
- SKIN COLOR
- SWEATING
- BLOOD PRESSURE
AUTONOMIC DYSREGULATION

- Fast or slow heart rate
- Inappropriate sweating
- Blood pressure
- Skin color
- High / low / unstable temp
- Gut & bladder function
AUTONOMIC FUNCTIONS

- FAST OR SLOW HEART RATE
- INAPPROPRIATE SWEATING
- BLOOD PRESSURE
- SKIN COLOR
- HIGH / LOW / UNSTABLE TEMP
- GUT & BLADDER FUNCTION
AUTONOMIC DYSREGULATION

- FAST OR SLOW HEART RATE
- INAPPROPRIATE SWEATING
- SPONTANEOUSLY PALE, FLUSHED, MOTTLED
- BLOOD PRESSURE
- HIGH / LOW / UNSTABLE TEMP
- GUT & BLADDER FUNCTION
AUTONOMIC FUNCTIONS

- Fast or slow heart rate
- Inappropriate sweating
- Spontaneously pale, flushed, mottled
- Blood pressure
- High, low, unstable temperature
- Gut & bladder function
AUTONOMIC DYSREGULATION

- Fast or slow heart rate
- Dizziness, fatigue, irritability
- Inappropriate sweating
- Spontaneously pale, flushed, mottled
- High, low, unstable temp
- Gut & bladder function
AUTONOMIC FUNCTIONS

- Fast or slow heart rate
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GUT & BLADDER FUNCTION
AUTONOMIC DYSREGULATION

- Fast or slow heart rate
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Problems with gut & bladder function
Autonomic symptoms run together for bad and for good.
Why are organic acidemias like mitochondrial disorders?
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ANAPLEUROSIS

LEU → 2-KETOISOCAPROIC ACID

ISOVALERYL CoA

3-METHYLCROTONYL CoA

3-METHYLGLUTACONYL CoA

3-OH-3-METHYLGLUTARYL CoA

ACETOACETATE + ACETYL CoA → KREBS CYCLE
ILE - VAL - MET - THR

GUT BACTERIAL PROPIONATE

CHOLESTEROL SIDE CHAINS

ODD CHAIN FATS

PROPIONYL CoA

METHYLMALONYL CoA

Succinyl CoA

KREBS CYCLE
Causes of low energy

Inadequate supply of substrate to the Krebs cycle → inadequate ATP supply
Components

- High acid / high ammonia / low glucose
- Toxic accumulation(s)
- Significant deficiency(ies)
- Overall energy deficiency
- Impact from the triggering event (infection)
- Iatrogenic worsening
Causes of low energy

Inadequate supply of substrate to the Krebs cycle $\rightarrow$ inadequate ATP supply

Poisoning of the energy production system $\rightarrow$ inadequate ATP supply
Urine organic acids (propionic acidemia)

Evidence of mitochondrial dysfunction

Lab session 1
Organic acidemias are not PRIMARY MITOCHONDRIAL DISORDERS

The have SECONDARY MITOCHONDRIAL DYSFUNCTION, and can behave like mitochondrial disorders
A case of methylmalonic acidemia

A 22 year old woman delivers a male at 37 weeks gestation following an unremarkable pregnancy, labor, and delivery. The baby was alert upon delivery. Weight measured 6-1/2 lb. Breast-fed well on day 1, then circumcised; afterwards, felt cold. By day 2, began to feed poorly, became hypoglycemic, transferred to the nursery. IV glucose given. Blood pH=7.27. Electrolytes showed a bicarbonate of 7, repeat 5. Intubated for transport, and given IV bicarbonate.
Upon arrival in the NICU, poorly responsive, jaundiced, with a deep labored breathing.

Labs:
- Bicarbonate 8, anion gap 32
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- Ammonia 96 µmol/L (NL<95), repeat 212
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The baby underwent dialysis. After placement of dialysis lines, repeat ammonia measured 1480 µmol/L. After two cycles - ammonia 586.

Urine organic acids - marked elevation of methylmalonic acid

*Diagnosis* - *methylmalonic acidemia*
EPILOGUE:

- Showed developmental delays (cognitive>motor) by 1-2 years of age
- Gastrostomy tube placed at 9 months to ensure adequate nutrition and taking of medications
- Relatively few metabolic crises, mild severity
- By 4 years, was not tolerating feeds consistently; slow gastric emptying and gastroesophageal reflux noted, so jejunostomy tube placed
- Central line placed at 4 years for IV blood draws and access
EPILOGUE (continued):

- By 5 years - liver and/or kidney transplantation considered → combined liver-kidney transplant. Good recovery without complications
- Improvement of fatigue and gut motility for 6-12 months, then progression
- Developed temperature (heat>cold) intolerance, random pallor/flushing, high heart rate/low blood pressure requiring higher fluid intake
- Relatively few metabolic crises, mild severity

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EPILOGUE (continued):

• By 8 years, parenteral (IV) nutrition added because of unreliability of GI tract
• By 11 years, on total parenteral nutrition due to gut failure
• At 13 years - cerebral atrophy, basal ganglia changes (MRI)
• At 16 years - diagnosed with diabetes mellitus
### Organic acidemias vs Mitochondrial disease

<table>
<thead>
<tr>
<th>Abnormal biochemistry</th>
<th>Organic acidemias</th>
<th>Mitochondrial disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lactate, Krebs cycle intermediates, 3-methylglutaconic acid</td>
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</tr>
</tbody>
</table>

<table>
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<tr>
<th>MRI findings</th>
<th>Organic acidemias</th>
<th>Mitochondrial disease</th>
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<tr>
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<td>Basal ganglia lesions</td>
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<table>
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<th>Cellular energetics</th>
<th>Organic acidemias</th>
<th>Mitochondrial disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced energy expenditure</td>
<td>Decreased oxygen extraction</td>
<td>Reduced energy expenditure Decreased oxygen extraction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>Organic acidemias</th>
<th>Mitochondrial disease</th>
</tr>
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<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
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</table>

<table>
<thead>
<tr>
<th>Respiratory chain dysfunction</th>
<th>Organic acidemias</th>
<th>Mitochondrial disease</th>
</tr>
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<tbody>
<tr>
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MMA KIDNEY - ABNL MITOCHONDRIA

ABNL MITOCHONDRIAL FUNCTION IN OAs

- Reduced cytochrome oxidase activity in liver in propionic and methylmalonic acidemia (Hayasaka et al, 1982)
- Reduced energy expenditure in patients with propionic and methylmalonic acidemia (Feillet et al, 2000)
- Inhibition of mitochondrial electron transport chain activities in rat brain by methymalonic acid (Brusque et al, 2002)
- Decreased OXPHOS activity in liver, kidney, heart, muscle in PA and MMA (de Keiser KY et al, 2009)
ABNL MITOCHONDRIAL FUNCTION IN OAs

- Propionate metabolites may inhibit pyruvate and 2-ketoglutarate dehydrogenase and deplete key compounds in the Krebs cycle (acetyl CoA, oxaloacetate, succinyl CoA) (Schreiber et al, 2012)
- Decreased electron transport enzyme activity in MMA mouse model (mut-/-) (Chandler RJ et al, 2009)
- Cardiac muscle in PA - OXPHOS dysfunction, decreased coenzyme Q10 (Fragaki K et al, 2011)
- In PA, documented mitochondrial dysfunction, increased reactive oxygen species and oxidative damage. Oral treatment with MitoQ or resveratrol shows benefit (Rivera et al, 2017)
PATHOGENESIS OF ORGANIC ACIDEMIAS

Components

High acid / high ammonia / low glucose
Toxic accumulation(s)
Significant deficiency(ies)
Overall energy deficiency
Impact from the triggering event (infection)
Iatrogenic worsening
## APPROACH TO TREATMENT

<table>
<thead>
<tr>
<th>Mitochondrial disease</th>
<th>No treatment at present, but it is coming...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic therapy for...</td>
<td>Organ-specific disease Autonomic dysfunction</td>
</tr>
<tr>
<td>Supplements</td>
<td>Coenzyme Q10 N-acetylcysteine Others</td>
</tr>
</tbody>
</table>

- CARDIOMYOPATHY
- HEARING LOSS
- DIABETES
- HYPOTHYROIDISM
- OTHER

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