Pyruvate Dehydrogenase Complex Deficiency

A Case Study

June 1, 2016  PRESENTED BY: Kate Schlag, MPH
Meet DD

- 11-year-old white male
- Seen in keto clinic with lead ketogenic pediatric dietitian and pediatric neurologist
- Adopted; currently lives with new foster mother
- Has been on and off MAD-4:1 ketogenic diet for a few years due to unstable home life
PMHx/Social hx

- Adopted at 4 months; born 6 weeks early
- Met development milestones late
- In PT/OT/speech therapy until age 3
- Kindergarten: diagnosed as being on autistic spectrum
PMHx/Social hx

- July 2013: went to bed “normal” and woke up “looking like he has cerebral palsy”
  - Dragging left foot
  - Falls a lot
  - Tires easily
  - Chokes easily
  - Staring spells
PMHx/Social hx

• November 2013
  – Convulsive episodes
  – Does not like eating; recently hospitalized for placement of G-tube due to dehydration and acidosis
  • Nutrition mostly from G-tube; eats only bananas and string cheese
Diagnosis (medical)

- Mitochondrial cytopathy: presumed pyruvate dehydrogenase complex (PDHc) deficiency

- MRI 9/9/13: 2 adjacent focal areas of altered signal within globus pallidus of right basal ganglia, potentially reflecting mild chronic changes associated with pyruvate dehydrogenase deficiency; suggestion of mild elevation of lactate and lipid peaks on MR spectroscopy

- Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures, without mention of intractable epilepsy

- Autism (most likely mediated by PDHc deficiency)
Agenda

1. Explanation of pyruvate dehydrogenase complex deficiency

2. Nutrition Assessment

3. Nutrition Diagnosis

4. Nutrition interventions, monitoring, and evaluation

5. Medical and nutritional outcomes

6. Discussion
Agenda

1. Explanation of pyruvate dehydrogenase complex deficiency

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6. Discussion
Pyruvate dehydrogenase complex deficiency

• Neurodegenerative disorder associated with abnormal mitochondrial metabolism; malfunction of citric acid cycle makes carbohydrates unable to be used as fuel source

• Associated with more than 55 different mutations
Pyruvate dehydrogenase complex

Pyruvate dehydrogenase, $E_1$

Dihydrolipoyl transacetylase, $E_2$

Dihydrolipoyl dehydrogenase, $E_3$
Pyruvate dehydrogenase complex

Three prosthetic groups:
- Thiamine pyrophosphate
- FAD
- Lipoic Acid

Two carriers:
- Coenzyme A
- NAD
Glucose (sugar) → Pyruvate → Acetyl-CoA → Mitochondria → Pyruvate Dehydrogenase Complex → Lactate
Buildup of lactate
CNS, cells deprived of fuel
Seizures
Pyruvate Dehydrogenase Complex Deficiency

- Characterized by buildup of lactic acid (which can worsen symptoms) and severe energy deficit (deprivation of ATP)
- Magnitude of energy deficit depends on residual activity of enzyme
  - Severe: congenital bran malformation d/t lack of energy during neural development; earlier onset; more rapid progression into widespread CNS damage (15-20% PDHc activity)
  - Milder: intermittent ataxia most prominent neurological symptom; 30-50% residual PDHc activity
Pyruvate Dehydrogenase Complex Deficiency

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Common Symptoms

• Poor muscle tone, poor acquisition or loss of motor milestones
• Neurological damage (brain cell injury, cognitive delays, seizures)
• Poor feeding
• Lethargy
Common Symptoms

- Poor muscle tone, poor acquisition or loss of motor milestones
- Neurological damage (brain cell injury, cognitive delays, seizures)
- Poor feeding
- Lethargy
Agenda

1. Explanation of pyruvate dehydrogenase complex deficiency

2. **Nutrition Assessment**

3. Nutrition Diagnosis

4. Nutrition interventions, monitoring, and evaluation

5. Medical and nutritional outcomes

6. Discussion
Social history

• Adopted; recently started with new foster family

• Foster mother lives in house that also has 20-year-old twins with cerebral palsy, 15-year-old, and 6-year-old foster child

• 1-2 staff at home each day for 6-8 hours; 24-hour coverage by staff on weekends
NCP: Nutrition Assessment

- Height: 159 cm (5'2.6") (97%)
- Weight: 48.8 kg (107 lb 9.4 oz) (89%)
- Weight for age: 89%
- BMI: 19.3
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Z-score</th>
<th>Δ Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>44.20</td>
<td>2.15</td>
<td></td>
</tr>
<tr>
<td>57.56</td>
<td>2.84</td>
<td>+.69</td>
</tr>
<tr>
<td>58.23</td>
<td>2.80</td>
<td>-0.04</td>
</tr>
<tr>
<td>58.19</td>
<td>2.77</td>
<td>-0.03</td>
</tr>
<tr>
<td>44.20</td>
<td>1.84</td>
<td>-.93</td>
</tr>
<tr>
<td>47.30</td>
<td>1.86</td>
<td>+0.02</td>
</tr>
<tr>
<td>50.50</td>
<td>2.04</td>
<td>+.18</td>
</tr>
<tr>
<td>47.30</td>
<td>1.71</td>
<td>+.33</td>
</tr>
<tr>
<td>48.30</td>
<td>1.73</td>
<td>+0.02</td>
</tr>
<tr>
<td>48.80</td>
<td>1.30</td>
<td>-.43</td>
</tr>
<tr>
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</tr>
<tr>
<td>------------</td>
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<td>-----------</td>
</tr>
<tr>
<td>147.3</td>
<td>2.51</td>
<td></td>
</tr>
<tr>
<td>146.2</td>
<td>2.27</td>
<td>-0.24</td>
</tr>
<tr>
<td>147.9</td>
<td>2.37</td>
<td>+0.10</td>
</tr>
<tr>
<td>147.8</td>
<td>2.27</td>
<td>-0.10</td>
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<tr>
<td>148.8</td>
<td>2.11</td>
<td>-0.16</td>
</tr>
<tr>
<td>151.6</td>
<td>2.12</td>
<td>+0.01</td>
</tr>
<tr>
<td>155.3</td>
<td>2.61</td>
<td>+.49</td>
</tr>
<tr>
<td>151.2</td>
<td>1.80</td>
<td>-0.81</td>
</tr>
<tr>
<td>152.0</td>
<td>1.79</td>
<td>-0.01</td>
</tr>
<tr>
<td>159.0</td>
<td>2.00</td>
<td>+.21</td>
</tr>
</tbody>
</table>
BMI, 2-20, CDC
## Pediatrics Malnutrition Criteria (>2 years)

<table>
<thead>
<tr>
<th>Anthropometric Criteria</th>
<th>At risk/Mild Malnutrition</th>
<th>Moderate Malnutrition</th>
<th>Severe Malnutrition</th>
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<tbody>
<tr>
<td>Weight-for-age z score</td>
<td>-1 to -1.9</td>
<td>-2 to -2.9</td>
<td>-3 or less</td>
</tr>
<tr>
<td>Height-for-age z score</td>
<td>No data</td>
<td>No data</td>
<td>-3 or less (may indicate stunting)</td>
</tr>
<tr>
<td>Weight for length or BMI z score</td>
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### Anthropometric Criteria: Change in body weight over time

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<tr>
<td>Deceleration in Weight-for-age z score</td>
<td>Decline of 1</td>
<td>Decline of 2</td>
<td>Decline of 3</td>
</tr>
<tr>
<td>Height-for-age Weight loss</td>
<td>5% of usual weight</td>
<td>7.5% usual weight</td>
<td>10% usual weight</td>
</tr>
<tr>
<td>Deceleration in Weight-for-length/BMI z score</td>
<td>Decline of 1</td>
<td>Decline of 2</td>
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<tbody>
<tr>
<td>Inadequate intake</td>
<td>51-75% of estimated calorie/protein needs</td>
<td>26-50% of estimated calorie/protein needs</td>
<td>≤25% of estimated calorie/protein needs</td>
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<td>Depleted fat stores: orbital, buccal, triceps, ribs. Bone prominences, loose/hanging skin, defined muscular outlines, minimal space when pinching</td>
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<td></td>
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Does DD meet any criteria for malnutrition?
Nutrition Focused Physical Exam

• Well-nourished; no signs of muscle or fat wasting

• Intermittent abdominal distention

• Wears braces on ankles
Pediatrics Malnutrition Criteria (>2 years)

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<td></td>
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Does DD meet any criteria for malnutrition? **No**
Diet history

• Has been on and off MAD-4:1 for past 3 years
  – In previous home, reports eating “anything and everything” and not doing tube feedings

• Recently switched to new foster home
  – Has been doing mostly tube feedings + few unmeasured amounts of very low carb foods
Diet history

• Previously in care of adoptive parents; non-compliant with prescriptive ketogenic diet

• Since being in foster care, foster mother has only been feeding him low carbohydrate foods and tube feedings (KetoCal 4:1)
# Lab overview (3/10/16)

<table>
<thead>
<tr>
<th>Overview</th>
<th>DD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketones, plasma</td>
<td>40 mg/dL</td>
<td>negative</td>
</tr>
<tr>
<td>Ketones, urine</td>
<td>80 mg/dL</td>
<td>negative</td>
</tr>
<tr>
<td>β-hydroxybutyrate</td>
<td>60 mg/dL (high)</td>
<td>0.0-3.0 mg d/L</td>
</tr>
<tr>
<td>Lipid profile good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No excessive acidosis (CO₂ = 20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Biochemical Genetics</th>
<th>DD</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Free Carnitine</td>
<td>17 (low)</td>
<td>22-63 umol/L</td>
</tr>
<tr>
<td>Acyl Carnitine</td>
<td>47 (high)</td>
<td>3-28 umol/L</td>
</tr>
<tr>
<td>Acyl/Free ratio</td>
<td>28 (high)</td>
<td>.1-.9</td>
</tr>
</tbody>
</table>
## Lab overview (3/10/16)

<table>
<thead>
<tr>
<th></th>
<th>DD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td>7</td>
<td>6-20 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.44</td>
<td>0.42-0.71 mg/dL</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.4</td>
<td>0.3-1.2 mg/dL</td>
</tr>
<tr>
<td>ALT</td>
<td>22</td>
<td>≤60 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>28</td>
<td>≤47 U/L</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>199</td>
<td>170-415 U/L</td>
</tr>
</tbody>
</table>
Noted labs upon diagnosis (2/27/13)

<table>
<thead>
<tr>
<th></th>
<th>DD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>3.1 (high)</td>
<td>0.6-2.3 mmol/L</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>0.147</td>
<td>0.08-0.16 mmol/L</td>
</tr>
<tr>
<td>Lactate: pyruvate ratio</td>
<td>21 (high)</td>
<td>8-20</td>
</tr>
</tbody>
</table>
Medications

• Alpha lipoic acid*
• Levocarnitine*
• B6*
• Thiamine*
• Fluoxetine (Prozac)
• Oxcarbazepine (antiepileptic)
• Calcium, vitamin D, MVI

*standard treatment for PDHc deficiency
Pyruvate dehydrogenase complex

Three prosthetic groups:
- Thiamine pyrophosphate
- FAD
- Lipoic Acid

Two carriers
- Coenzyme A
- NAD
Estimated Nutrition Needs

• 1,460-1950 kcal (30-40 kcal/kg per OHSU ketogenic guidelines)
  – Calories generally started at 85% RDA
  – Developmental delay guidelines: initial calories should be based on usual intake/current TF

• Protein: 36.6 g (.75 g/kg)
Agenda

1. Explanation of pyruvate dehydrogenase complex deficiency

2. Nutrition Assessment

3. Nutrition Diagnosis

4. Nutrition interventions, monitoring, and evaluation

5. Medical and nutritional outcomes

6. Discussion
NCP: Diagnosis (1)

- Impaired nutrient utilization related to altered nutrient-related lab values as evidenced by lactate:pyruvate ratio of 21 and elevated lactate of 3.1 umol/L
NCP: Diagnosis (2)

• Excessive carbohydrate intake for specific disease state related to limited adherence to nutrition related recommendations as evidenced by lactate:pyruvate ratio of 21
NCP: Diagnosis (3)

• Increased nutrient needs for total fat intake to induce ketosis related to ketogenic therapy as evidenced by seizure activity
Agenda

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2. Nutrition Assessment
3. Nutrition Diagnosis
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6. Discussion
Medical treatment

- Seizures under good control with diet therapy and oxcarbazepine monotherapy
  - Continue oxcarbazepine at current dose
  - Written seizure precautions

- Dietary management per ketogenic pediatric dietitian
  - If substantial increase in seizures, check urine ketones; given compliance issues, may be helpful
  - Mental health support
NCP: Intervention

- Modified Atkins Diet/Ketogenic Diet
What is a ketogenic diet?

• High-fat, low-carbohydrate diet

• When body is deprived of carbohydrates, fats become the primary fuel

• Ketones are formed when the body uses fat for its source of energy
Fatty Acids →

- Glucose
- Alanine → Pyruvate
- Pyruvate → Lactate
- Pyruvate dehydrogenase complex → Acetyl CoA
  - Lipids
  - Ketone bodies
  - Krebs cycle

Mitochondrial membrane

NCP: Intervention
Fatty Acids → Provide alternate fuel source

- Glucose
- Alanine
- Pyruvate
- Lactate
- Mitochondrial membrane
- Pyruvate dehydrogenase complex
- Acetyl CoA
- Lipids
- Ketone bodies
- Krebs cycle

NCP: Intervention
# Ketogenic Diet: Recommended

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dairy products</td>
<td>35-40% heavy whipping cream</td>
</tr>
<tr>
<td>Fats</td>
<td>Butter</td>
</tr>
<tr>
<td></td>
<td>Any vegetable oil low in sat fat</td>
</tr>
<tr>
<td></td>
<td>Margarine and mayonnaise (carb-free, low in sat fat, trans fat free)</td>
</tr>
<tr>
<td></td>
<td>Nuts (calculate carbohydrate content in diet)</td>
</tr>
<tr>
<td>Fruits and Vegetables</td>
<td>All fruits and vegetables</td>
</tr>
<tr>
<td>Protein foods</td>
<td>Red meats, eggs, poultry, seafood</td>
</tr>
<tr>
<td>Beverages</td>
<td>Plain water</td>
</tr>
<tr>
<td></td>
<td>Sugar-free beverages</td>
</tr>
<tr>
<td></td>
<td>Herbal tea</td>
</tr>
</tbody>
</table>
# Ketogenic Diet: Not Recommended

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Not Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread and cereal products</td>
<td>All, unless it can be calculated into individual’s meal plan</td>
</tr>
<tr>
<td>Dairy products(^1)</td>
<td>Sweetened yogurt, plain yogurt, milk, cheese</td>
</tr>
<tr>
<td>Fats</td>
<td>Dressings containing sugar Gravies with carb ingredients</td>
</tr>
<tr>
<td>Fruits and Vegetables</td>
<td>Fruits packed in syrup Dried or candied fruit</td>
</tr>
<tr>
<td>Protein foods</td>
<td>None</td>
</tr>
<tr>
<td>Beverages</td>
<td>Fruit juices or punch, soft drinks, regular tea or coffee</td>
</tr>
</tbody>
</table>

\(^1\) Unless it can fit into individual’s meal plan
What is a Modified Atkins Diet (MAD)?

- Less restrictive form of ketogenic diet

- How is it different?
  - No fluid or calorie restriction/limitation
  - Fats strongly encouraged but not weighed/measured
  - No restrictions on proteins (in some cases)
How does ketogenic diet help with PDHc deficiency?

• Unknown; proposed mechanisms
  – Reduction in blood and intracellular lactate and pyruvate
  – Increase of circulating free fatty acids, β-hydroxybutyrate and acetoacetate provides alternate fuel source for CNS and other tissues
  – Alters energy metabolism in brain, reducing excitability
NCP: Intervention

• Modified Atkins Diet/Ketogenic Diet
  – <10 g carbs per day
  – 3 meals and 1-2 snacks per day
  – Should be drinking ~2,000 mL fluid per day
NCP: Intervention

• Modified Atkins Diet/Ketogenic Diet
  – <10 g carbs per day
  – 3 meals and 1-2 snacks per day
  – Should be drinking ~2,000 mL fluid per day
  – If refuses meal, provide 1 full box Ketocal 4:1 formula
NCP: Intervention

• 4:1 ratio of fat:carbs+protein

• Main ingredients are refined vegetable oils and milk protein (casein and whey)

• DHA + ARA
NCP: Intervention

- Snack ideas
  - ¼ cup cashews
  - 2 oz original beef jerkey
  - Carb master yogurt
  - 5 slices bacon
NCP: Intervention

- Enteral Feeds if not eating
  
  - Daytime: 3x per day: 5.5 oz (165 ml)
    Ketocal 4:1 liquid + 6 oz water
  
  - Nighttime feeds: 22.5 oz (675 ml) Ketocal 4:1 liquid + 325 ml water; run pump @ 100 mL per hour x 10 hrs
  
  - Feeds to provide 2000 kcal, 2072 mL free water
NCP: Intervention

- Education

  - Nutrition relationship to health and disease

  - Emphasized importance of avoiding carbohydrates because of negative impact on cognitive function and health
NCP: Intervention

• Short-term goals

  – Improve compliance with ketogenic diet

  – *Heavily dependent on stable home life/new foster parents*
NCP: Intervention

• Long-term goals
  – Reduce seizure activity to prevent immediate, acute worsening of disease
  – Delay progression of disease and damage
NCP: Monitoring & Evaluation

- Weight and growth
- Intake
- Physical activity
- TF tolerance
- Bowel regularity
NCP: Monitoring & Evaluation

• Labs

– 1 month: BMP, β-hydroxybutyrate, acetoacetate, urinalysis

– 3 month: CMP, fasting lipid panel, zinc, selenium, Vitamin D, calcium, creatinine, CBC, β-hydroxybutyrate, acetoacetate, urinalysis

– 6 month: acylcarnitine profile, zinc, selenium, vitamin D, calcium creatinine, CBC, β-hydroxybutyrate
Agenda

1. Explanation of pyruvate dehydrogenase complex deficiency

2. Nutrition Assessment

3. Nutrition Diagnosis

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5. Medical and nutritional outcomes

6. Discussion
Outcome: medical

• Prognosis is unclear because of the small number of children with PDHc deficiency studied and large number of mutations involved

• Complications: seizures and CNS deterioration
Outcome: medical

• DD has milder case of PDHc deficiency

• Uncle with suspected PDHc deficiency passed away in adulthood; likely that DD has similar prognosis
Outcome: medical

- No generalized treatment for PDHc deficiency at this time
Outcome: nutritional

• Goal of ketogenic diet

1. Reduce glucose utilization and increase ketone body production by mitochondrial beta-oxidation

2. Shift from glycolysis toward increased citric acid cycle activity and direct mitochondrial metabolism of ketone bodies
“Management is still far from ideal although early institution of a KD may be helpful in some cases”

—AN Prasad, Associate Professor of Pediatrics in Neurology
Outcome: nutritional

- Most data used to support KD in PDHc deficiency “are based on a few uncontrolled case reports, in which dietary composition varied widely”

—PDHc deficiency results from at least 55 different mutations; very likely that treatment and success vary tremendously
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Discussion

• What went well?

  – Treatment at OHSU with specialized doctors and dietitians

  – New foster mother who shows a dedicated interest in DD’s health
Discussion

• Room for improvement
  – Earlier identification and treatment of disease
  – Better treatment from initial adoptive parents
Discussion

- Room for improvement
  - Earlier identification and treatment of disease
  - Better treatment from initial adoptive parents

*Treatment is most beneficial if started early*
Future Directions

• Right now, treatment is unsatisfactory and most patients fail to respond to medications

• Development of medications that target specific gene → influence whole epileptic gene network

• In families with history of PDHc deficiency, prenatal treatment with ketogenic diet may reduce brain damage that would otherwise occur in prenatal period
Thank You

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References


References


