Not Your Typical Case of Ketotic Hypoglycemia
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Objectives
By the end of this session, attendees should be able to:
1. Discuss the difference between idiopathic ketotic hypoglycemia and an underlying disorder causing ketotic hypoglycemia.
2. Describe the process for evaluating ketotic hypoglycemia.
3. Explain the modes of genetic inheritance for certain disorders causing ketotic hypoglycemia.

No conflicts of interest.
What is Ketotic Hypoglycemia (KH)?

Normal Fasting Time

<table>
<thead>
<tr>
<th>Age</th>
<th>Fasting Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>12 Hours</td>
</tr>
<tr>
<td>Infant</td>
<td>24 Hours</td>
</tr>
<tr>
<td>Child</td>
<td>36 Hours</td>
</tr>
<tr>
<td>Adult</td>
<td>48+ Hours</td>
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Several Terms - Same Thing
- Ketotic Hypoglycemia
- Idiopathic Ketotic Hypoglycemia
- Idiopathic Hypoglycemia of Childhood

KH Typical Presentation
- Young child with an illness
  - Vomiting and poor POs
  - Symptoms of hypoglycemia
  - ER – hypoglycemia and ketonuria
  - Often a one-time episode

Repeated KH
- Child characteristics
  - Thin
  - Poor eater
  - Fewer stores of fat and glycogen
  - Any illness or longer fast will cause ketosis and hypoglycemia
KH Treatment and Prognosis

- Well controlled with dietary changes
  - Limited fasting time
  - Mixed meals
  - Uncooked cornstarch (1-2 grams/kg)
- Typically resolves by school age
- Rarely causes seizures/brain damage

Not all cases of ketotic hypoglycemia are of this typical variety.

Case Study

- “Greg” is a 5 10/12 year old Caucasian boy with symptoms of hypoglycemia
- Symptoms
  - Always first thing in the morning
  - Irritability, abdominal pain, nausea, tachycardia, and frequently vomiting
  - Mom has noticed feeding him alleviates symptoms
Case Study
• Mild Symptoms Resolve in 15 minutes
• Severe Symptoms Last 4+ hours
• Fasts 11 hours overnight
• Eats a snack before bed of carbs/protein

Past Medical History
• Symptoms began at 2 years old
• Off and on for the past 3.5 years
• Normal cognitive and motor development
• No seizures
• No access to insulin, anti-diabetes medications, alcohol, or beta blockers

Family History
• Maternal uncle and 2 distant maternal cousins (both boys) have had similar symptoms
• Uncle
  • Symptoms resolved by age 13
  • No intellectual disabilities nor obvious health problems
Greg’s Physical Exam

• No abnormalities
• No hepatomegaly
• Normal growth

Growth Charts

Weight 75th percentile
Height 75-90th percentile

Evaluation

• Home blood sugar and ketone monitoring
• Home → At time of symptoms
  ◦ Hypoglycemia (BS=50s)
  ◦ Ketonuria (Moderate to Large)
• Recommended a diagnostic fasting test
• Why?
Time Lapse

... 15 months later...

Now 7 years old

Insurance issues
Symptoms seemed better
Then symptoms returned

Evaluation

- Inpatient diagnostic fasting test
  - 11.5 hours with BS > 70 mg/dL
  - 13.5 hours total

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Diagnostic Fasting Lab Results

<table>
<thead>
<tr>
<th>Component (reference range)</th>
<th>Result</th>
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<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (&lt;1)</td>
<td>49 mg/dL</td>
<td>Lactate (&lt;2)</td>
<td>0.4 mmol/L</td>
</tr>
<tr>
<td>Lactate (&lt;1)</td>
<td>&lt;1.0 mmol/L</td>
<td>C-peptide (&lt;0.5)</td>
<td>0.1 ng/mL</td>
</tr>
<tr>
<td>ROHE (&gt;2.5)</td>
<td>2.5 mmol/L</td>
<td>Ammonia (0-31)</td>
<td>&lt;9 mmol/L</td>
</tr>
<tr>
<td>FFA (&gt;2.5)</td>
<td>1.4 mmol/L</td>
<td>Total Carnitine (35-84)</td>
<td>&lt;9 mmol/L</td>
</tr>
<tr>
<td>Cortisol (&gt;15)</td>
<td>17.0 mcg/dL</td>
<td>Free Carnitine (24-63)</td>
<td>&lt;9 mmol/L</td>
</tr>
<tr>
<td>Growth Hormone (&gt;10)</td>
<td>0.2 ng/ml</td>
<td>Acylcarnitine profile and Urine Organic Acids</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Results: Normal*
### Additional Lab Results

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<tr>
<th>Component</th>
<th>Reference Range</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>(0.7-5.97)</td>
<td>1.88 uIU/ml</td>
</tr>
<tr>
<td>Free T4</td>
<td>(0.85-1.75)</td>
<td>1.71 ng/dL</td>
</tr>
<tr>
<td>IGF-1</td>
<td>(113-284)</td>
<td>163 ng/mL</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>(2-4-2)</td>
<td>4.0 mcg/mL</td>
</tr>
<tr>
<td>ALT</td>
<td>(10-25)</td>
<td>20 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>(15-37)</td>
<td>28 U/L</td>
</tr>
</tbody>
</table>

### Fasting Test Summary
- Abbreviated fasting time for age
- No hyperinsulinism
- No fatty acid oxidation disorder
- Abbreviated fasting time + elevated liver enzyme + family history + age = not typical ketotic hypoglycemia

### What Could It Be?
- Genetic Disorders that cause ketotic hypoglycemia:
  - Glycogen Storage Disease 0 (Glycogen Synthase Deficiency)
  - Glycogen Storage Disease III (Debrancher Deficiency)
  - Glycogen Storage Disease VI (Phosphorylase Deficiency)
  - Glycogen Storage Disease IX (Phosphorylase Kinase Deficiency)
  - Growth Hormone and/or Cortisol Deficiency
  - Other rare genetic disorders
Growth Hormone/Cortisol Deficiency?
- Normal cortisol level when hypoglycemic
- Normal growth
- Normal growth factors
- Normal thyroid function

Very Unlikely

Glycogen Storage Disease?
- Difficult to differentiate types
- Untreated GSDs typically associated with:
  - hepatomegaly
  - poor growth
- Greg did not have these

What to do?
- Confident not GH deficiency
- Some features of GSDs
  - KH
  - Mildly elevated liver enzyme
- Family history
**Genetic Evaluation**

- GSD NextGen Sequencing Panel (Prevention Genetics)
  - Screens for all types of GSD with one sample
  - Cheaper and quicker than testing 1 type of GSD at a time
- Newer Test – Metabolic Hypoglycemia NextGen Sequencing Panel
  - 21 genes – all types of GSD plus other rare disorders that cause KH

**Genetic Results**

- + for variant in PHKA2 - predicted to be disease causing
- PHKA2 is a gene that encodes phosphorylase kinase
- Located on the X chromosome
- This is an X-linked form of GSD IX

**Example of X-linked Inheritance**

![Diagram of X-linked inheritance]
Family Testing

- Maternal Uncle who also had symptoms has the same PHKA2 mutation
- Mom is an obligate carrier
- Sister could be a carrier – not yet tested

Phosphorylase Kinase Deficiency

- GSD IX
- Along with GSD VI (phosphorylase deficiency), account for 25% of all cases of GSD

GSD IX - Clinical Features Variable

- Ketotic hypoglycemia
- Growth retardation/short stature
- Weakness
- Fatigue
- Motor delay
- Hepatomegaly
- Mild hyperlipidemia
- Elevated liver enzymes
- Hepatic fibrosis and cirrhosis
- Hepatic adenomas
Phosphorylase Kinase (PK)
- Present in Liver and Muscle
- 4 subunits (α, β, γ, δ)
- 3 different genes encode PK
  - PHKA2(α) – Liver only – X-linked – 75% of all cases
  - PHKB(β) – Liver and muscle – recessive inheritance
  - PHKG2(γ) – Liver only – recessive inheritance
  - No mutations identified in the δ subunit gene


PK Action

- Treatment
  - Uncooked cornstarch 0.6-2.5 grams/kg as needed to prevent ketogenesis
    - Ketones should remain <1mM/L
  - High protein diet
    - 2.5 gm/kg
  - Avoid large quantities of simple sugars
  - Limit fasting time
  - Treatment lessens with age

## Surveillance for GSD IX

- Home BS and ketone measurement
- Yearly evaluation
  - Liver enzymes
  - Lipids
  - Growth parameters
  - Liver ultrasound

## Follow-up on Greg

- High protein diet
- Avoid concentrated sugar
- Bedtime
  - Uncooked cornstarch ~1 gram/kg
  - Snack
- No further symptoms of hypoglycemia
  - FBSs normal and Ketones negative

## Summary

- KH can be caused by an underlying genetic disorder
- Genetic testing warranted when KH associated with:
  - Short fasting time
  - Older child
  - Poor growth
  - Elevated liver enzymes
  - Hepatomegaly
Questions?

- Has anyone had cases of ketotic hypoglycemia that do not seem idiopathic?
- Have you had cases of a genetically identified cause for ketotic hypoglycemia?

References


