Beyond the Naked Eye: A Case Presentation on a Rare Form of Congenital Hyperinsulinism (HI)

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Patient Demographics

- **Patient:** 3 yo Hispanic girl transferred from the midwest for evaluation of hyperinsulinism following
- **Birth Hx:**
  - 36 weeker, LGA, born via VBAC,
  - no complications at birth and no notable hypoglycemia
- **PMH:**
  - RSV
  - Recurrent UTI, mild/mod enlarged kidneys on u/s-no hydronephrosis, VCUG negative

Patient Demographics

- **FMH:**
  - Paternal GGM: diabetes
  - Mother: anemic
  - Father: reflux
  - Siblings: 2 older brothers healthy
Hypoglycemia Evaluation at OSH

- Additional history
  - At 2 yo seizure after sleeping 11 hours
  - At PCP Fasting BG = 25 mg/dL and insulin = 3.21 uU/mL
  - Fasted 10 hours and BG fell to 42 mg/dL

- Critical sample:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG</td>
<td>42 mg/dL</td>
<td>70-100 mg/dL</td>
<td></td>
</tr>
<tr>
<td>BOHB</td>
<td>0.26 mmol/L</td>
<td>&lt;0.6 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>3.1 uU/mL</td>
<td>&lt;2 uU/mL</td>
<td></td>
</tr>
<tr>
<td>C-peptide</td>
<td>0.33 mg/mL</td>
<td>&lt;0.1 mg/mL</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>11.5 mg/mL</td>
<td>&gt;10 mg/mL</td>
<td>Passed</td>
</tr>
<tr>
<td>GH</td>
<td>0.77 ng/mL</td>
<td>&lt;10 ng/mL</td>
<td>Passed</td>
</tr>
</tbody>
</table>

- Glucagon-Stim: 42 to 76 mg/dL Positive

- Treated with diazoxide and octreotide

Fasting in Children with Normal Glucose Metabolism

Brain Metabolism (%)

- Glycogenolysis
- Ketogenesis
- Gluconeogenesis

Glycogen Storage Disease (GSD) Type 1 F-1,6-Pase deficiency
Ethanol
Hyperinsulinism
Hypoglycemia
-
Normal
- Fatty acid oxidation defect

Hypoglycemia

- Acidemia
  - ↑ Lactate
  - ↑ Ketones

- No Acidemia
  - ↑ FFA Ketones

Glycemic response to glucagon

Hyperinsulinism Mimickers:
- Bartter-Wiedemann Syndrome
- Congenital Disorders of Glycosylation
- Neonatal Paraplegia
- Insulinoma
Hypoglycemia Evaluation at CHOP

- **To Confirm HI Diagnosis:**
  - Repeat diagnostic fast

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood sugar 70-100 mg/dL</th>
<th>BOHB &gt; 3 mmol/L</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hours</td>
<td>&gt; 70 mg/dL</td>
<td></td>
<td>Slow dextrose</td>
</tr>
<tr>
<td>44</td>
<td>&lt; 0.33</td>
<td></td>
<td>In 40 minutes</td>
</tr>
</tbody>
</table>

- **Genetic Testing:** HI genetic testing negative (x6 genes)

**Diagnosis of HI**
1. BG less than 50 mg/dL
2. Suppressed BOHB
3. Elevated insulin or c-peptide
4. Positive response to glucagon

Hypoglycemia Management Plan

- **Management:**
  - Patient failed medical therapy with her primary endocrine team
    - Diazoxide 1st line therapy
    - Octreotide 2nd line therapy
      - Diazoxide d/c/d
      - Managed on IV Dextrose

- **Plan:**
  - PET
  - Surgery

How Beta cells produce insulin
Common Surgical Forms of HI

CHOP Congenital HI Center Statistics
Surgical Patients (N=433):
- Diffuse: 43%
- Focal: 50%
- Atypical: 7%
  - Localized Islet Cell Nuclear Enlargement: 2.5%
  - Beckwith-Wiedemann Syndrome: 3%
  - Turner Syndrome: 1.5%

Hypoglycemia Management Plan

- **Imaging**: 18 F-DOPA PET scan negative
  - Special isotope that targets neuroendocrine cells in the pancreas
  - Differentiates between diffuse vs focal HI
  - 85% sensitivity
  - 98% specificity
- **Surgery**: Underwent 40% distal pancreatectomy for localized islet cell nuclear enlargement (L.I.N.E)
Nucleomegaly: more prominent in sections from tail

Localized islet cell nuclear enlargement (L.I.N.E.)

- Islet cell nucleomegaly similar to diffuse HI but confined to specific region(s) of pancreas
  - Otherwise normal islets elsewhere
  - Older infants at age of presentation
  - Clinical improvement with partial pancreatectomy

Hypoglycemia Management Plan

Post-Op Course

- Full PO feeds within 1 week of surgery
- Cure fast after 5 days of monitoring on full feeds
- She lasted 18 hours, 12 hours >70 mg/dL. BG at the end of the fast was 49 mg/dL with BOHB of 2.1 mmol/L

Criteria for Cure
1. BGs >70 mg/dL for 12 hours.
2. BOHB above 2 mmol/L.
3. No response to glucagon

Cured!
CHOP Data for L.I.N.E. Type HI

• 11 cases
  – None had detectable genetic mutation found in blood sample
  – 9 have undergone NGS sequencing on the pancreatic tissue
  – Genetic mutations found in 5/9
    • 2 GCK
    • 3 ABCC8 (most common genetic form of HI)
    • 2/4 that remain negative no pancreatic tissue available

Conclusions

• HI is a complex disease that requires further research to improve diagnosis and management options
• Genetic testing on blood samples may not be sensitive enough to pick up all mutations
• Genetic mutations may be detected in pancreatic tissue leading to surgical treatment and cure!
• HI patients may require referral to a HI center with expertise in imaging, and medical and surgical management

References: