WHAT IS CAUSING THIS HYPOGLYCEMIA?
THE STORY OF ONE HOT MESS!
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CONFLICT OF INTEREST DISCLOSURE
• No conflicts of interest
CASE STUDY
5 year old African-American female presented to our Endocrinology Clinic with hypoglycemia

DD’S MEDICAL HISTORY
- Abnormal chromosomes -
  - Duplication of 11q13.5-11p14.1 affecting 5 genes
- Obstructive Hydrocephalus
- VSD - surgically repaired at one month of age
- Cortical visual impairment
- Bilateral hearing loss
- Hypotonia
- Seizure disorder
- GERD - Gastro-esophageal Reflux Disease
  - Nissen Fundoplication surgery at 4 months of age
- Chronic respiratory failure
- Profound intellectual disability

CURRENT MEDICAL STATUS
- Tracheostomy - ventilator dependent
- Fed solely via gastrostomy tube
- Resides in a long term care facility for children
HYPOGLYCEMIA

- First 18 months of life, several low blood glucose (BG) levels with routine blood work
- Meter BGs:
  - Continuous feedings = no low BGs
  - Bolus feedings = frequent low BGs between boluses (50-65mg/dL; 2.8-3.6mmol/L)
- What number constitutes a low BG?
  Answer: <70mg/dL (3.9mmol/L)
- Are you concerned that DD is having low BGs?
  Answer: Yes
  Why?
  Answer: Low BG can cause further brain damage

LOW BLOOD GLUCOSE

- 18 months to 5 years:
  - Outpatient visits with 2 different Endocrinology groups
  - Unable to admit her due to:
    - Insurance issues
    - Medical complications
  - Safe on continuous feedings
  - At 5 years old, admission for diagnostic testing to determine
    What is Causing This Hypoglycemia?
**DIAGNOSTIC EVALUATION**

**FASTING TEST**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Glucose</td>
<td>47 mg/dL</td>
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<tr>
<td>Lactate</td>
<td>0.8 mM/L</td>
</tr>
<tr>
<td>FFA</td>
<td>1.41 mM/L</td>
</tr>
<tr>
<td>BOHB</td>
<td>1.7 mM/L</td>
</tr>
<tr>
<td>Insulin</td>
<td>&lt;1 uIU/mL</td>
</tr>
<tr>
<td>CO₂</td>
<td>29 mM/L</td>
</tr>
</tbody>
</table>

**FINDINGS**

- Hypoketotic Hypoglycemia
  - No glycogen storage disease
  - No fatty acid oxidation disorder
  - Too much insulin
- Could she have Congenital Hyperinsulinism?
  - No - did not fit criteria for this diagnosis
- What about her chromosome 11 duplication?
  - No association with hyperinsulinism

**ANYTHING ELSE FROM PMH?**

Nissen Fundoplication
**NISSEN FUNDOPICATION**

Popular method of surgical management of severe GE reflux in infants and children

90% success rate in controlling reflux

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**DUMPING SYNDROME**

- First described in 1978
- Up to 30% of children develop dumping syndrome after Nissen fundoplication
- Dumping syndrome can be classified as:
  - "Early dumping" (30 min after meal): CV and GI symptoms
  - "Late dumping" (1-3 hrs after meal): hypoglycemia symptoms

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**MECHANISM RESPONSIBLE FOR PPH AFTER NISSEN FUNDOPICATION**

- Gastric relaxation and accelerated gastric emptying
- Rapid emptying of osmotic load into small intestine
- Absorption of carbohydrates
  - Hyperglycemia
  - Hyperinsulinemia
  - Hypoglycemia

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PPH AFTER NISSEN FUNDOPICATION
- Immediate to several years after surgery
- Presenting symptoms: lethargy, diaphoresis, tachycardia, irritability, pallor
- Frequently unrecognized cause of new onset seizures or increased frequency of pre-existing seizures


PPH RESEARCH
- Protocol to screen for PPH postoperatively after Nissen Fundoplication
- n=285
- Of those screened, 24% diagnosed with PPH
- Of those not screened, 1.3% diagnosed with PPH
- Hyperglycemia preceded PPH in 67.7%


ORAL GLUCOSE TOLERANCE TEST

Charts used with permission from D. DeLeón, MD.
GLP-1 Function

- Food into stomach
- GLP-1 release
- Potentiates insulin release from beta cells
- Inhibits glucagon secretion
- Inhibits gastric emptying
- Suppresses appetite
- Inhibits glucose production from the liver

GLP-1 and PPH Research

- Children with PPH after Nissen fundoplication who undergo an OGTT or Formula TT have:
  - Glucose
  - Insulin
  - GLP-1
- Exaggerated compared with controls
- Represents an association, not causation
- Important for treatment options

**OGTT - 1.75GM/KG**

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**DD EVALUATION**

- **Fasting Test:**
  - Hypoketotic hypoglycemia
  - Hyperinsulinemia

- **How do we evaluate for PPH from Late Dumping Syndrome?**
  - Oral Glucose Tolerance Test (OGTT)
  - Formula Tolerance Test (FTT)

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**DD FORMULA TOLERANCE TEST**

<table>
<thead>
<tr>
<th>Time(min)</th>
<th>Glucose(mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>88</td>
</tr>
<tr>
<td>+30</td>
<td>103</td>
</tr>
<tr>
<td>+60</td>
<td>132</td>
</tr>
<tr>
<td>+90</td>
<td>111</td>
</tr>
<tr>
<td>+120</td>
<td>91</td>
</tr>
<tr>
<td>+150</td>
<td>77</td>
</tr>
<tr>
<td>+180</td>
<td>44</td>
</tr>
</tbody>
</table>

Nutren Junior 250mL bolus
**DIAGNOSIS**

- PPH secondary to Dumping Syndrome
- Diagnostic criteria: low BG levels (<60mg/dL) post-bolus on 2 separate occasions


**TREATMENT**

- Feeding manipulations
  - Continuous intragastric feedings
  - Low carbohydrate or high fiber
  - Longer feedings

- Insulin suppression
  - Diazoxide (Proglycem®)
  - Octreotide (Sandostatin®)
  - Neither has been successful in preventing PPH


- Alpha-glucosidase inhibitor
  - Delays conversion of long chain to short chain sugars
  - Postprandial increase in blood sugar

Effective dose in children with PPH after Nissen:
- 25, 50, or 75 mg per meal - start at 25mg
- Give with the start of each meal/bolus

**ACARBOSE (PRECOSE®)**

- Alpha-glucosidase inhibitor
  - Delays conversion of long chain to short chain sugars
  - Postprandial increase in blood sugar
  - Effective dose in children with PPH after Nissen:
    - 25, 50, or 75 mg per meal - start at 25mg
    - Give with the start of each meal/bolus

- Side effects:
  - Diarrhea, malabsorption, abdominal discomfort
  - Elevation of liver enzymes - check every 6-12 months

ACARBOSE BLUNTS INSULIN RESPONSE AND PREVENTS HYPOGLYCEMIA

- Initial response excellent
- Not sustained -
  - Persistent hypoglycemia despite
    - Increasing dose of acarbose
    - Prolonging her bolus time
    - Adding fiber to her formula
- Switched back to continuous feeds

DD FORMULA TT WITH AND WITHOUT ACARBOSE

DD RESPONSE TO ACARBOSE
Hospitals that perform surgical fundoplasty should have a protocol for PPH screening.

**Protocol:**
- Full feedings
- BGs q. 30 minutes X 2 hours X 3 days > discharge
- For BG<60, consult Endocrinology

**Timing of presentation variable**

**Repetition of PPH variable**

**Control of PPH with acarbose may not be sustained**

**Families must know BG monitoring and low BG treatment**

**HYPOGLYCEMIA TREATMENT FOR PPH**

- If BG<60mg/dL:
  - 10-15 grams of complex carbohydrate enterally
  - Connect to continuous formula feeding for 30 minutes
  - Recheck BG in 20 minutes
- If child is unresponsive with low BG:
  - Give 2cc/kg D10 via G-tube or IV
  - Glucagon 1mg SQ, IM, IV
- A continuous formula or dextrose infusion may be needed to maintain normal glucose levels
SUMMARY

- PPH is a frequent complication of surgical Nissen fundoplication
- Biochemical characterization:
  - Earlier and higher glucose rise
  - Subsequent drop by 2-3 hours
  - Δ Insulin
  - Δ GLP-1
- Treatment options
  - Acarbose
  - Feeding manipulation

SUMMARY

- PPH after Nissen is one of the only hypoglycemia disorders that causes non-fasting hypoglycemia
- When evaluating a child for hypoglycemia, be sure to ask about surgical history of Nissen Fundoplication