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)

LOW BLOOD GLUCOSE

- 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

EVALUATION

- 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

Glucose	47 mg/dL
Lactate	0.8 mM/L
FFA	1.41 mM/L
BOHB	1.7 mM/L
Insulin	<1 uIU/mL
CO_2	29 mM/L

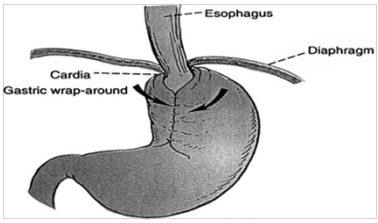
FINDINGS

- 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 FUNDOPLICATION



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

90% success rate in controlling reflux

Esposito C. et al. Surg Endosc. 2006; 20(6); 855-858.

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**

Villet, et al. Chir Pediatr 1978; 19: 269-73; Samuk et al. J Pediatr Gastroeterol Nutr 1996; 23:235-40; Rivkees, S. et al. Pediatrics 1987; 80: 937-42.

MECHANISM RESPONSIBLE FOR PPH AFTER NISSEN FUNDOPLICATION

⇩ gastric relaxation and accelerated gastric emptying

↓

Rapid emptying of osmotic load into small intestine

↓

⇧ absorption of carbohydrates

↓

Hyperglycemia

↓

Hyperinsulinemia

↓

Hypoglycemia

Vu M.K. et al. Am J Gastroenterol 1999; 94: 1481-9; Gitzelmann R. et al Eur J Pediatr 1986; 145:504-6.

PPH AFTER NISSEN FUNDOPLICATION

- 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

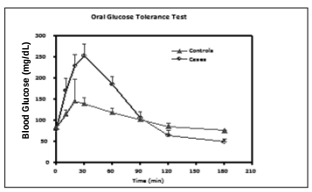
Ng, et al. J Pediatr, 2001; 139:877-9.

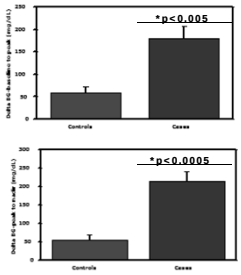
PPH RESEARCH

- 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%

Calabria, A.C. et al. J Pediatr 2011; 159:597-601.

ORAL GLUCOSE TOLERANCE TEST





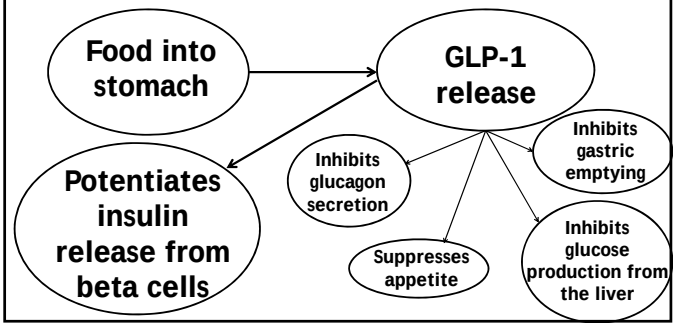
Charts used with permission from D. DeLeón, MD.

GLP-1

Glucagon-like Peptide-1

Hormone released by intestinal L cells

GLP-1 FUNCTION



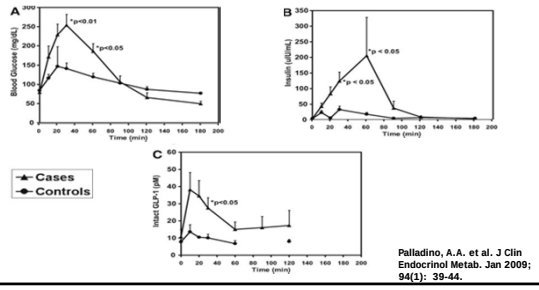
GLP-1 AND PPH RESEARCH

- **Children with PPH after Nissen fundoplication who undergo an OGTT or Formula TT have:**
  - ⇧Insulin
  - ⇧GLP-1

  ...exaggerated compared with controls
- **Represents an association, not causation**
- **Important for treatment options**

Palladino, A.A. et al. J Clin Endocrinol Metab. Jan 2009; 94(1): 39-44.

OGTT - 1.75GM/KG



Palladino, A.A. et al. J Clin Endocrinol Metab. Jan 2009; 94(1): 39-44.

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)**

DD FORMULA TOLERANCE TEST

Time(min)	Glucose(mg/dL)
0	88
+30	103
+60	132
+90	111
+120	91
+150	77
+180	44

Nutren Junior 250mL bolus

DIAGNOSIS

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

Calabria, A.C. et al. J Pediatr 2011; 159:597-601.

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

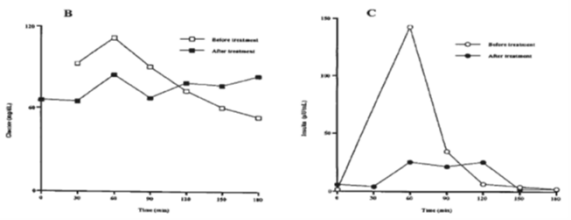
Borovoy J. et al. Am J Gastroenterol 1998; 93:814-8; Samuk, I. et al. J Ped Gastroenterol Nutr 1996; 23:235-40; Lehnert H. et al. Arch Intern Med 1990; 150: 2401-2; Khoshoo V. et al. Arch Dis Child 1991; 66:1447-8.

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 a each meal/bolus
- Side effects
  - Diarrhea, malabsorption, abdominal discomfort
  - Elevation of liver enzymes – check every 6-12 months

Ng, et al. J Pediatr, 2001; 139:877-9.

ACARBOSE BLUNTS INSULIN RESPONSE AND PREVENTS HYPOGLYCEMIA



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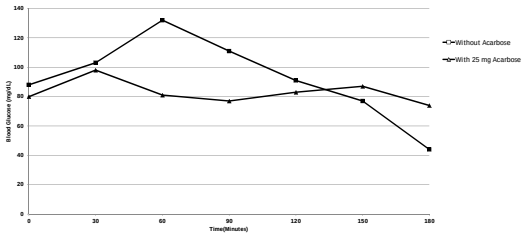
DD FORMULA TT WITH AND WITHOUT ACARBOSE



DD RESPONSE TO ACARBOSE

- 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

SCREENING FOR PPH

- 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

UNIQUE FEATURES OF PPH

- 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
  - ⇧Insulin
  - ⇧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