Diazoxide-responsive Hyperinsulinism

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Outline

- Definition of diazoxide-responsiveness
- Genetic mutations in diazoxide-responsive hyperinsulinism
- Treatment of diazoxide-unresponsive hyperinsulinism
Diazoxide-responsiveness

- Able to wean intravenous dextrose
- Able to maintain normal plasma glucose during:
  - Normal feeding schedule
  - Overnight fast
Diazoxide-Responsive HI

- Common Genetic
  - GDH-HI (HI-HA Syndrome)
  - KATP-HI

- Very common non-Genetic
  - Perinatal-Stress HI

- Rarer Genetic
  - HNFs-HI
Frequency of diazoxide-unresponsive hyperinsulinism

**HI Panel**  
N = 782

- **Diazoxide Responsive**  
  n = 263 (34%)
- **Diazoxide Unresponsive**  
  n = 451 (58%)
- **Syndromic-HI**  
  n = 68 (8%)

- **SURGICAL**  
  n = 415 (92%)
- **NON-SURGICAL**  
  n = 36 (8%)

- **FOCAL HI**  
  n = 207 (50%)
- **DIFFUSE HI**  
  n = 192 (46%)
- **LINE HI**  
  n = 13 (3%)
- **ATYPICAL**  
  n = 3 (1%)

‡ = ABCC8, KCNJ11, GCK, GLUD1  
§ = add’l genes: HNF4A, HNF1A, HADH, UCP2

Children with hyperinsulinism seen at CHOP between 1997-2015
Genotype of 705 children (1997-2014)

- Diazoxide-Unresponsive (434)
  - Focal (1 rec $K_{ATP}$)
  - Diffuse (2 rec $K_{ATP}$)
  - Diffuse (1 dom GCK)
  - No mutations

- Diazoxide-Responsive (219)
  - Focal (1 rec $K_{ATP}$)
  - (mostly $K_{ATP}$ mutations)
  - 1 dom GLUD1
  - 1 dom $K_{ATP}$
  - No mutations
  - 2 rec SCHAD
  - 1 dom UCP2
  - 1 dom HNF4A
  - 1 dom HNF1A
KATP-HI: the most common genetic form of hyperinsulinism

- Caused by inactivating mutations of SUR1 or Kir6.2 (ABCC8, KCNJ11) on chromosome 11p
- **Four clinical types**
  1. **Recessive mutations**: Diffuse HI, severe neonatal onset hypoglycemia, diazoxide non-responsive
  2. **Focal adenomatosis**: Focal HI; clinically indistinguishable from severe recessive KATP-HI; paternally-derived recessive KATP mutation **PLUS** maternal 11p LOH; curable by surgery(!)
  3. **Dominant mutations** (severe): Diffuse HI, severe neonatal onset hypoglycemia, diazoxide non-responsive
  4. **Dominant mutations** (mild): Diffuse HI, later-onset milder hypoglycemia, diazoxide responsive (surgery not needed)
**$K_{ATP}$ Channels**

Diabetes risk and channel activity are associated with different types of $K_{ATP}$ channels.

- Neonatal Diabetes
- E23K diabetes risk
- Dominant KATP HI
- Recessive KATP HI

**Mg-ADP** and **diazoxide** increase channel activity, while **ATP** and **tolbutamidine** decrease it.
KATP HI mutations: Recessive or Dominant Inheritance

- delPhe1388 homozygous
- p.delSer1387 heterozygous
Dominant Diazoxide-responsive KATP HI

Figure 1
Pedigrees of 16 children with dominant hyperinsulinism associated with K_ATP channel mutations. The pedigrees are labeled in ascending order of age at presentation.
**Dominant diazoxide-responsive \( K_{ATP} \) Hyperinsulinism**

- Fasting hypoglycemia
- Protein-induced hypoglycemia
- Diffuse – no need for PET

<table>
<thead>
<tr>
<th>Subtype</th>
<th>BW</th>
<th>Age of presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recessive (-) Dz (n=48)</td>
<td>87% LGA</td>
<td>1 day (1-9)</td>
</tr>
<tr>
<td>Dom (-) Dz (n=17)</td>
<td>65% LGA</td>
<td>1 day (1-180)</td>
</tr>
<tr>
<td>Dom (+) Dz (n=13)</td>
<td>77% LGA</td>
<td>30 days (1-1215)</td>
</tr>
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Glucose Response to Oral Protein Tolerance Test

Blood Glucose (mg/dL)

KATP HI  GDH HI  controls
Prolonged hypoglycemia in neonates: “Perinatal stress hyperinsulinism”

- Associated with erythroblastosis*, IUGR**, birth asphyxia**, toxemia, infant of diabetic mother***
- Glucose requirement up to 20-30 mg/kg/min
- Duration few days up to 3 months; remits spontaneously
- No benefit from glucocorticoids
- Responds well to diazoxide Rx
- Mechanism unknown, but is very common (10% of SGA****)

*Raivio, Osterlund, 1969 Pediatrics
**Collins & Leonard, Lancet 1984; ADC 1990
***Hoe, et al. 2006 J Pediatr
****Palotto, et al. 2004
Perinatal-Stress HI: Spontaneous Resolution of Hyperinsulinism
(n = 24, m±SEM)

<table>
<thead>
<tr>
<th>Resolution of Perinatal Stress Hyperinsulinism</th>
<th>At Diagnosis</th>
<th>After Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (µU/mL)</td>
<td>6.2±1.2</td>
<td>3.0±0</td>
</tr>
<tr>
<td>BOB (mM)</td>
<td>0.8±0.2</td>
<td>2.6±0.1</td>
</tr>
<tr>
<td>FFA</td>
<td>0.6±0.1</td>
<td>1.7±0.2</td>
</tr>
<tr>
<td>Glucagon response (mg/dL)</td>
<td>40±3</td>
<td>11±3</td>
</tr>
</tbody>
</table>
HI due to Inactivating Mutations in HNF4A-HI & HNF1A-HI (MODY1 & MODY3) (dominant monogenic diabetes)

- Hepatic Nuclear Factor transcription factors control organ-specific gene expression in liver, kidney, islets
- Dominant mutations of HNF4a and HNF1A cause HI in infancy evolving to insulinopenic diabetes in adulthood
- HNF4a carrier infants: LGA, diazoxide-responsive HI
- HNF1A carrier infants: not so LGA, but also have diazoxide-responsive HI
- Mechanism of HI (?): partial KATP channel deficiency (decreased expression of Kir6.2) and/or altered expression of other genes (e.g., UCP2)
- MODY1 and MODY3 diabetes very responsive to glyburide
HNF1A: p.Y218X

- 2 affected brothers
- paternal AODM in lousy control
- DM much better after switch to glyburide

### Family Tree

#### I
- a [n/n]
- b [n/n]

#### II
- a [n/n]
- b [n/n]
- c
- d

#### III
- 3
- a [n/n]
- b [n/n]
- c [n/n]
- d [n/M]
- e
- f [n/M]
- g [n/M]

#### IV
- a [n/M]
- b [n/M]

n = wild type
M = HNF1A: p.Y218X

- hypoglycemia confirmed
- hypoglycemia suspected
- diabetes
## Variation in Duration of Hypoglycemia in HNF4A – HI (n = 26)

<table>
<thead>
<tr>
<th>Duration of HI</th>
<th>Number of Cases (%)</th>
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<tbody>
<tr>
<td>&lt; 1 month</td>
<td>12 (46%)</td>
</tr>
<tr>
<td>3-6 months</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>12 (46%)</td>
</tr>
</tbody>
</table>

Kapoor, James, Hussain. in Monogenic Hyperinsulinemic Hypoglycemia Disorders. Front Diabetes (Karger), vol 21, pg 182, 2012
How do we manage diazoxide-responsive hyperinsulinism

1. Diagnosis of HI
2. 5 day trial of Diazoxide
   - Safety Fast with BS > 70 mg/dL (3.8 mmol/L)
   - Diazoxide Responsive
     - Continue Diazoxide
     - Outpatient follow-up: labs, glucose monitoring
     - Inpatient admission every 1-2 years for safety fast +/- OPTT
3. Send genetic testing
Safety Fast

- To ensure that children can fast safely for extended period of time
  - (8-12 hours) neonates/infants
  - (18) HI-diazoxide responsive
- Performed prior to full endocrine evaluation OR when endocrine cause has been identified to establish safety on home regimen
- End for BG <60, BOHB 3 x2, Time or s/s
- Labs: ACP, UOA
OPTT

- NPO 4 hours
- 3 hour test: q15 min for first hr, then q30 min
- For HI patients-diagnostic or routine
- Protein load (1.16 gm/kg of resource powder) given to determine if they have protein sensitive HI (both KATP mutations and HI/HA)
- End for BG <50 or severely symptomatic
- Labs: BG, insulin, ammonia (0 and 60 min)
- Check for allergies-milk protein
FASTING TOLERANCE

Your child will be fasted prior to discharge to determine safe fasting tolerance. The time given is a guide to help you determine when your child needs to eat and/or take medication(s).

This time is arbitrarily cut in half when sick and again is a guide to help you manage glucose levels.

Your child will be periodically admitted in the hospital for a safety fasting test to determine parameters for home management.
Normal Fasting Tolerance

- Newborn - 12-18 hours
- Infant - 24 hours
- Child - 36 hours
- Adult - 48-72 hours
HOME MANAGEMENT

Blood glucose monitoring: Check glucose levels as instructed (usually first AM; before feeds and when symptomatic). If obtaining levels less than 70 mg/dL – repeat and if still less than 70 mg/dL – feed your child with a recheck in glucose within 20 -30 minutes. Repeat until glucose is above 70 mg/dL.

If your child can’t consume enough food to increase glucose level (sick; vomiting; too weak or having a seizure) give glucagon injection. Recheck glucose level within 20 – 30 minutes and go to your local hospital (glucagon last about 1 hour)
Cure Fast

• Evaluation of HI patients who have had surgery or who were considered transient HI
• Same fasting criteria as the diagnostic fast, but only obtain an HI draw
  – BG, BOHB, insulin, c-peptide, IGFBP1, FFA
• End for BG<50, BOHB 3x2, Time, s/s
ER MANAGEMENT

Prior to discharge, you will be given an ER letter to take with you to local hospitals.

If unable to maintain glucose levels greater than 70 mg/dL and you need to seek ER management, please take your letter with you for assistance.

SCHOOL MANAGEMENT

You can request a letter to be given to the school nurse outlining management guidelines for your child while in school and/or daycare.
FEEDING GUIDELINES

Eat 3 meals and snacks a day--every day. Your child’s body needs food for energy and growth. Skipping meals is not healthy. A regular pattern of eating helps keep blood sugars stable.
Some examples of healthy foods containing complex carbohydrates:
Spinach Whole Barley Grapefruit Turnip Greens Buckwheat Apples Lettuce Buckwheat bread Prunes Water Cress Oat bran bread Apricots, Dried Zucchini Oatmeal Pears Asparagus Oat bran cereal Plums Artichokes Museli Strawberries Okra Wild rice Oranges Cabbage Brown rice Yams Celery Multi-grain bread Carrots Cucumbers Pinto beans Potatoes Dill Pickles Yogurt, low fat Soybeans Radishes Skim milk Lentils Broccoli Navy beans Garbanzo beans Brussels Sprouts Cauliflower Kidney beans Eggplant Soy milk Lentils Onions Whole meal spelt bread Split peas, nuts
Some examples of foods containing simple carbohydrates:
Table sugar, Corn syrup, Fruit juice, Candy, Cake, Bread made with white flour, Pasta made with white flour, Soda, Candy, All baked goods made with white flour and most packaged cereals
MEDICATIONS

DIAZOXIDE – blocks release of insulin in the beta cells of the pancreas.

DIURIL – helps to release the extra fluid retention caused by taking Diazoxide.

OCTREOTIDE – decreases the amount of insulin released by the beta cells of the pancreas.

GLUCAGON – a hormone that releases glucose from the liver stores into the bloodstream.
**Dosage:** 5 – 15 mg/kg/day in 2 divided doses  
**NOTE:** Need 5 days to reach therapeutic level.

**Monitoring parameters:** Blood pressure, serum glucose, serum uric acid, CBC, diff/plts and comprehensive metabolic panel.

**Dosage form:** oral suspension 50 mg/mL

**Side effects:** edema (puffiness) and hypertrichosis (hairy)
Chlorothiazide (Diuril)

- **Dosage:** Use same guidelines as Diazoxide, otherwise, refer to CHOP formulary for range.
- **Monitoring Parameters:** weight, blood pressure, accurate I/O’s, basic metabolic panel.
- **Dosage Form:** oral suspension 250 mg/5 mL
- **Side effects:** hypotension (low blood pressure); electrolyte changes (Na/K)
GLUCAGON

**Dose:** 1 mg IM  
**Monitoring parameters:** glucose and BP  
**Dosage form:** emergency kit  
**Side effects:** hypotension
FOLLOW-UP GUIDELINES

PCP – 1 – 2 weeks after every hospital evaluation and as needed along with usual well child protocol.

Endocrinologist – 2 – 4 weeks after every hospital evaluation and then every 3 – 6 months. Call office with updates as needed.

Inpatient Evaluation – scheduled on each child’s individual as needed basis.

Neurodevelopmental Evaluation (Age 12 – 18 months and 5 years of age) – Early Intervention (OT/PT/Speech)
CHOP Hyperinsulinism Center

✓ http://www.chop.edu/service/congenital_hyperinsulinism-center/home.html

✓ 215-590-3174