Management of Glucose in the Preterm Infant

Charles A. Stanley, MD
Division of Endocrinology
Children's Hospital of Philadelphia
Disclosures
Charles Stanley, MD

• I have no relevant financial relationships to disclose or conflicts of interest to resolve.

• I will not discuss any unapproved or off-label, experimental or investigational use of a product or device.
The Problem

- Too little glucose: risk of seizures, permanent brain damage, liability suits
The Elephant and The Blind Men
Knowledge Gaps and Research Needs for Understanding and Treating Neonatal Hypoglycemia: Workshop Report from Eunice Kennedy Shriver National Institute of Child Health and Human Development

William W. Hay, Jr., MD, Tonse NK. Raju, MD, DCH, Rosemary D. Higgins, MD, Satish C. Kalhan, MBBS, FRCP, and Sherin U. Devaskar, MD

Unfortunately, untoward long-term outcomes in infants with one or two low blood glucose levels have become the grounds for litigation and for alleged malpractice.

Marvin Cornblath, 2000


This funding opportunity announcement (FOA) is issued by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) to encourage Research Project Grant (R01) applications from institutions and organizations to propose studies related to basic, applied and translational research in neonatal hypoglycemia. While much progress has been made in understanding the causes and mechanisms of altered neonatal glucose homeostasis, major gaps remain. Through this

Concerns about neonatal hypoglycemia driven by malpractice worries.
IN KEEPING with tradition concerning the choice of subject for a presidential address, I originally prepared a semiphilosophical dissertation for this occasion. Now, I must apologize to you for the sin of "deviation," because I suddenly decided only a few days ago to scrap that laboriously composed oration and substitute a résumé of some observations that my associates and I have made during the past few years in dealing with the clinical problem of spontaneous hypoglycemia in infants.

My seemingly impulsive decision to change to the latter title was the direct result of my seeing the seventh young child, among a series of cases recently examined in our clinic, who had suffered irreparable brain damage from severe hypoglycemia. Three of these were children who were victims of the misuse of insulin in the treatment of diabetes mellitus. The remaining four were examples of severe spontaneous hypoglycemia in infants who were victims of delayed diagnosis and inadequate early therapy.

The tragedy of permanent brain damage resulting from therapeutically induced hypoglycemia * is too well known and the precautions necessary for its avoidance are too obvious to justify special consideration at this time. The situation is quite different, however, in regard to the special group of infants with spontaneous hypoglycemia which I have felt compelled to discuss here today. There have been well-documented cases of brain damage associated with spontaneous hypoglycemia.†
Fig. 3.—Photograph of J. G., aged 6 years, and B. G., aged 15 months. Taken two months after beginning of corticotropin therapy. Pancreatic resection scars visible.
Idiopathic Hypoglycemia: Concerns in 1953

1. Irreparable brain damage

2. Delayed diagnosis

3. Inadequate (early) therapy

4. Etiology

5. Genetic?
How have we been doing since the time that Idiopathic Hypoglycemia of Infancy was described in 1953?

Not Great!:

For neonates with HI (the most common form of congenital hypoglycemia):

1. 30% of infants with focal HI who required pancreatectomy were not detected before discharge from nursery
2. 50% of diazoxide-responsive HI cases are not detected during the neonatal period.
3. Rates of neurodevelopmental delay in infants with congenital HI are too high (25-50% of cases).

Risk of lawsuits for poor outcomes associated with hypoglycemia remains a concern
Points to cover

- Use of “critical sample” for specific diagnosis

- Three different types of hypoglycemia in neonates:
  1. transient/developmental in normal neonates
  2. peri-natal stress/prolonged hyperinsulinism
  3. permanent/genetic forms (especially, HI)

- Focal vs Diffuse forms of congenital hyperinsulinism

- Hypoglycemia and normal newborns
(1) Permanent hypoglycemia in neonates: Hyperinsulinism (HI) is the most common cause.

CHOP series 1998-2002 (156 cases)

- HI needing surgery: 34%
- HI diazoxide responsive: 17%
- Transient HI: 26%
- β-Oxidation defects and Hypopituitarism: 19%
- Glycogenoses: 4%
Congenital Hyperinsulinism (HI)

✓ Incidence ~1 in 20,000
✓ LGA birthweight common
✓ Increased glucose utilization (GIR up to 20-30 mg/Kg/min)
✓ Recessive or dominant (9 loci)
✓ Treatment:
  • diazoxide
  • surgery (98% PX if diffuse, local excision if focal)

NB. Never use steroids for treatment of hypoglycemia!
Use of “Critical Samples” to Define Specific Etiology

Fasting Hypoglycemia

Acidemia

- Upward arrow (↑) Lactate
  - G-6-Pase
  - F-1,6-Pase
  - PCase
  - Ethanol

- Upward arrow (↑) Ketones
  - Normal
  - Ketotic Hypo
  - GSD 3,6,9,0
  - GH-def
  - Cortisol-def

No Acidemia

- Downward arrow (↓) FFA
- Upward arrow (↑) Ketones
  - FAO def

- Downward arrow (↓) Ketones
  - Hyperinsulinism
  - Cong Hypopit
  - SGA/birth asphyxia
  - ? Neonates DOL1

Glycemic response to glucagon
Hypoketonemia: a diagnostic feature of hyperinsulinemic-hypoglycemia

Fig. 2. Relationship of plasma glucose and β-hydroxybutyrate levels during fasting in infants with hyperinsulinism (diamonds), control infants (open circles), and children with ketotic hypoglycemia (closed circles). Regression lines, $y = a + bx$ (glucose mg/100 ml), were $y = 0.797 - (0.0067)x$, $r = -0.356, P > .1$. For infants with hyperinsulinism (broken line), $y = 5.58 - (0.066)x$, $r = -0.73, P < .001$ for controls, and $y = 4.12 - (0.044)x$, $r = -0.77, P < .001$ for children with ketotic hypoglycemia. The lines for the control and the ketotic hypoglycemic group were not significantly different ($P > .3$).

The common regression line is $y = 4.31 - (0.047)x$, $r = -0.76, P < .001$ (solid line).
Hypoketonemia better for diagnosing HI than insulin level.
Insulin vs β-Hydroxybutyrate at Blood Glucose < 50 mg/dl
Beta-hydroxybutyrate bedside monitoring

- Finger-stick enzymatic assay for BOB
- Range 0–6 mmol/L
- Accuracy ± 0.5 mmol/L
- Expected levels
  - Well-fed: <0.1 mmol/L
  - Hypoglycemia: >2.5 mmol/L
Diagnosis of Hyperinsulinism: Glycemic Response to Glucagon
Congenital Hyperinsulinism
Recessive or Dominant Inheritance
Congenital Hyperinsulinism: Genes

- glucose
- leucine
- amino acids
- glutamate

Mechanisms:

- GK
- MCT1
- mechanism unclear: SCHAD, HNF4a, UCP2
- pyruvate
- diazoxide
- $K_{ATP}$ channel SUR1 & KIR6.2

Ca++
- Insulin
- somatostatin
- tolbutamide

ATP
- depolarization
- GDH

Calcium channel
Focal HI

- Clinically identical to recessive, diffuse KATP-HI
- 40-70% of severe congenital HI cases
- Diazoxide unresponsive
- Surgical pancreatectomy required
- 2-hit mechanism:
  - Clonal LOH for maternal 11p
  - UPD for a recessive paternal KATP-channel mutation
HISTOLOGIC FORMS OF HYPERINSULINISM

Diffuse form

Focal form
Patients with Focal vs. Diffuse

- Focal: 44% (73)
- Diffuse: 56% (94)
Imaging focal HI by 18F-DOPA PET scan (Positron Emission Tomography)

- Usual imaging methods don’t work in focal HI (MRI, CT, Echo, catheterization)

- 18F-DOPA concentrated in beta-cells to form an image of focal lesion in the PET scan

- 18F-DOPA custom-made for PET scans in UPenn cyclotron under FDA investigational IND
Focal HI $^{18}$F-DOPA PET Scan
F-F-DOPA PET: Focal HI in Infant with Ectopic Lesions in Jejunum

10 min post injection

60 min post injection

(focal lesion in head of pancreas)

(small arrows show ectopic lesions in jejunum)
Interpreting Glucose Levels: Glucose Treatment Targets

Data from Cryer, et al.
Criteria for management of hyperinsulinism and other forms of hypoglycemia

- Cure of Focal HI: able to fast keeping BS >70 mg/dL for 18 hr OR ketones > 2.5 mM before BS <50 mg/dL

- Good control (e.g., diazoxide Rx in HI): same

- Adequate control of hypoglycemia for discharge: able to fast through 2+ feeds keeping BS >70 mg/dL (i.e., minimum 8-10 hr)
Outcomes of Focal Patients (94 cases)

- Cured/No Meds: 94% (88 cases)
- Not Cured: 6%

Outcomes of Diffuse Patients (73 cases)

- Controlled: 36% (26 cases)
- Required Medical Therapy for Hypoglycemia: 49% (36 cases)
- Required Insulin Therapy for Diabetes: 15% (11 cases)
Transient Neonatal Hypoglycemia (Day 1)

- High risk related to delayed feeding

- Mechanism: *speculative* (immaturities in hepatic ketogenesis & gluconeogenesis, insulin suppression until 12-24 hours)
Plasma Glucose Distribution Prior to 1st Feed at 8 hr of Age

Fig. 3. A normal distribution of glucose levels can be seen in full term AGA, post-term AGA and full term LGA data. There is a general shift toward lower levels in the preterm AGA group and a bimodal distribution in the term SGA group. Pr = Preterm. F = Term. Po = Post-term.
Incidence of Hypoglycemia before 1st Feed at 8hr old (BS < 30 mg/dL)

Fig. 1. Incidence of hypoglycemia in newborn infants, classified by birth weight and gestational age. Glucose levels <30 mg/100 ml prior to first feeding.

(Lubchenko & Bard, Pediatrics, 1971)
### Evolution of Transient Neonatal Hypoglycemia: Frequency of Plasma Glucose < 50 mg/dL Day 1 vs Day 2-3

(Lubchenko & Bard, Pediatrics, 1971)

<table>
<thead>
<tr>
<th></th>
<th>Term</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 1\textsuperscript{st} feed at 8 hr of age</td>
<td>29 %</td>
<td>50 %</td>
</tr>
<tr>
<td>Day 2-3 of life</td>
<td>0 %</td>
<td>1 %</td>
</tr>
</tbody>
</table>
Lack of ketogenic response to hypoglycemia in both AGA and SGA neonates on Day 1.


Fig 2. Relationship of plasma glucose and β-hydroxybutyrate levels at the end of the first postnatal fast in 44 newborn infants. AGA infants are indicated by solid circles; SGA infants are indicated by open circles. Regression line is $y = 0.145 + (0.002)x$, $r = +.23$, $P = .07$.


Congenital HI

On Day 1: Ketogenesis is suppressed in both normal and SGA neonates. (Haymond et al. NEJM 1974)
Hypoketonemia in Term Neonates during 1st week

Etiology of Transient Hypoketotic Hypoglycemia in Normal Neonates:

Immaturities of Fasting Adaptation

- **Hepatic Gluconeogenesis**:
  - PEP-CK activity absent
  - Matures by 12-24 hr
- **Hepatic Ketogenesis**
  - CPT-1 (& ?HMG-CoA synthase) absent
  - Expression activated by long-chain fatty acids (colostrum)
  - Matures by 12-24 hr
- **Insulin secretion**
  - Incomplete suppression at low BS
  - ? Persistent HK1, MCT1 expression

- **Implication**: All infants born with at least two strikes!
Prolonged Neonatal Hypoglycemia
(Day 2 up to several weeks)

- Birth asphyxia, SGA, maternal hypertension, other peri-natal stresses

- Mechanism: hyperinsulinism
Fig. 3. A normal distribution of glucose levels can be seen in full term AGA, post-term AGA and full term LGA data. There is a general shift toward lower levels in the preterm AGA group and a bimodal distribution in the term SGA group. Pr = Preterm. F = Term. Po = Post-term.
Incidence of Hypoglycemia before 1st Feed at 8hr old
(BS < 20 mg/dL)

Fig. 2. Incidence of hypoglycemia in newborn infants, classified by birth weight and gestational age. Glucose levels <20 mg/100 ml prior to first feeding.
Maternal preeclampsia appears to be a risk factor for prolonged hypoglycemia in SGA neonates during 1st 24 hr (open circles).

Fig. 1. Plasma glucose levels prior to feedings during the first day of life in early-fed SGA infants. Open circles denote plasma glucose values of infants of preeclamptic mothers.

Prolonged Hyperinsulinism in Perinatal Stress Hypoglycemia


### Characteristics of 26 neonates with peri-natal stress HI

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Frequency</th>
<th>( P ) value (vs US newborns 2000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>81%</td>
<td>0.005</td>
</tr>
<tr>
<td>Maternal hypertension</td>
<td>12%</td>
<td>0.3</td>
</tr>
<tr>
<td>Prematurity</td>
<td>23%</td>
<td>0.1</td>
</tr>
<tr>
<td>SGA</td>
<td>27%</td>
<td>0.01</td>
</tr>
<tr>
<td>LGA</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Perinatal stress</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>62%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No risk factors</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

### Features of prolonged neonatal hyperinsulinism (median, range)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of initial hypoglycemia</td>
<td>1 day (0 to 168 days)</td>
</tr>
<tr>
<td>Age at diagnosis of hyperinsulinism</td>
<td>13 days (2 to 180 days)</td>
</tr>
<tr>
<td>Maximum glucose infusion rate</td>
<td>12 mg/kg/min (0 to 19 mg/kg/min)</td>
</tr>
<tr>
<td>Treatment Required:</td>
<td></td>
</tr>
<tr>
<td>Frequent feeding only</td>
<td>5 neonates</td>
</tr>
<tr>
<td>Diazoxide Treatment</td>
<td>19 neonates</td>
</tr>
<tr>
<td>Continuous feeding</td>
<td>2 neonates</td>
</tr>
<tr>
<td>Age resolution documented</td>
<td>181 days (18 to 403 days)</td>
</tr>
</tbody>
</table>

Perinatal-Stress HI: Evidence of Hyperinsulinism that Spontaneously Resolves (n = 24, m±SEM)

<table>
<thead>
<tr>
<th></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>
**Perinatal-Stress HI: Acute Insulin Responses (AIR)**

( resembles GK-HI; ?overexpression of HK1)

(n = 11, m±SEM)

<table>
<thead>
<tr>
<th></th>
<th>Calcium</th>
<th>Leucine</th>
<th>Glucose</th>
<th>Tolbutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal-Stress</td>
<td>0.2 ± 0.5</td>
<td>2 ± 1</td>
<td>29 ± 6</td>
<td>23 ± 5</td>
</tr>
<tr>
<td>GK-HI (3)</td>
<td>-4</td>
<td>5</td>
<td>79,80</td>
<td>ND</td>
</tr>
<tr>
<td>KATP-HI (6)</td>
<td>22 ± 4</td>
<td>5 ± 2</td>
<td>14 ± 4</td>
<td>0.7 ± 1</td>
</tr>
<tr>
<td>GDH-HI (5)</td>
<td>-4 ± 2</td>
<td>73 ± 21</td>
<td>98 ± 24</td>
<td>70 ± 17</td>
</tr>
<tr>
<td>Normals (6)</td>
<td>0.1 ± 0.6</td>
<td>2 ± 3</td>
<td>42 ± 9</td>
<td>53 ± 12</td>
</tr>
</tbody>
</table>
Functional Properties of GK-HI & GK-MODY Mutations & Effect of HK1 Expression

![Graph showing glucose phosphorylating capacity vs blood glucose levels with different genotypes and mutations. The graph compares wild type, heterozygous M210K or T228M mutation, and homozygous M210K and T228M mutations, along with the effect of HK1 expression.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>WILD TYPE</th>
<th>M210K MUTATION</th>
<th>T228M MUTATION</th>
<th>ins454A mut</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turnover rate (sec⁻¹)</td>
<td>52.4±5.7</td>
<td>16.7±1.6</td>
<td>0.004±0.0004</td>
<td>45</td>
</tr>
<tr>
<td>Glucose $S_{0.5}$ (mmol/liter)</td>
<td>7.7±0.1</td>
<td>38.7±1.9</td>
<td>5.5±1.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Hill coefficient</td>
<td>1.66±0.00</td>
<td>1.63±0.04</td>
<td>0.71±0.07</td>
<td>1.2</td>
</tr>
<tr>
<td>ATP₉₅₀ (mmol/liter)</td>
<td>0.35±0.01</td>
<td>1.38±0.11</td>
<td>0.62±0.16</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Diurnal glucose profiles in severe (child 1) & mild (child 2) GCK-HI
(Mean plasma glucose 50±2 vs. 63±1 mg/dL, P < 0.0001)
Prolonged hypoglycemia in neonates: “Perinatal stress hyperinsulinism” ***

- Associated with SGA, birth asphyxia, toxemia*
- Common: 10% of SGA have hypoglycemic beyond 1 week of age
- Glucose requirement up to 20-30 mg/kg/min
- Spontaneous remission, but can last up to 3 months
- No benefit from glucocorticoids
- Usually responds well to diazoxide Rx
- Mechanism uncertain, but resembles GK-HI

*Collins & Leonard, Lancet 1984; ADC 1990
** Palotto, et al. 2004
*** Hoe, et al. 2006 J Pediatr
The Elephant and The Blind Men

[Diagram of an elephant being touched by two sticks labeled "Endo" and "Neo".]
Neonatal hypoglycemia

Hypoglycemia

Day 1
- no risk factors
  - asymptomatic
    - feed re-check
- risk factors
  - or symptomatic
    - IV dextrose re-check
      - keep glucose > 70
      - workup if can’t fast > 12 hr

Day 2+
- breast fed
  - feed re-check
- all others
  - IV dextrose re-check
    - keep glucose > 70
    - workup if can’t fast > 12 hr
Neonatal hypoglycemia take-home messages

- Need to be specific about type and mechanism
- After Day 1, Hyperinsulinism is the most frequent cause (peri-natal stress or genetic)
- Ketones are suppressed in neonatal hypoglycemia
- Glucose thresholds should be same as in older children (treatment target is to keep BS > 70 mg/dL)
- For medically-unresponsive hyperinsulinism, an experienced team approach is important to find & cure potential focal HI lesion
end
Glucose Thresholds

• Physiologically normal is 70-100 mg/dL
• Therapeutic target for hypoglycemia is to keep BS > 70 mg/dL
• End-point for provocative fasting test is BS < 50 mg/dL
• Same for newborns as older children/adults
# Phenotypes of Congenital Hyperinsulinism

<table>
<thead>
<tr>
<th></th>
<th>genetics</th>
<th>Sensitivity to stimuli / inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>diazoxide</td>
</tr>
<tr>
<td>KATP</td>
<td>rec</td>
<td>NO</td>
</tr>
<tr>
<td>KATP</td>
<td>dom</td>
<td>yes</td>
</tr>
<tr>
<td>GDH</td>
<td>dom</td>
<td>yes</td>
</tr>
<tr>
<td>GCK</td>
<td>dom</td>
<td>NO</td>
</tr>
<tr>
<td>SCHAD</td>
<td>rec</td>
<td>yes</td>
</tr>
<tr>
<td>MCT1</td>
<td>dom</td>
<td>?</td>
</tr>
<tr>
<td>HNF4a</td>
<td>dom</td>
<td>yes</td>
</tr>
<tr>
<td>UCP2</td>
<td>dom</td>
<td>yes</td>
</tr>
<tr>
<td>Peri-natal stress</td>
<td>dom</td>
<td>yes</td>
</tr>
</tbody>
</table>
Figure 1. Threshold Plasma Glucose Levels at Which Plasma Levels of Glucagon, Epinephrine, Growth Hormone, and Cortisol Increase, Cognition Is Impaired, and Symptoms of Hypoglycemia Occur in Normal Subjects.

Yellow bars represent data from Schwartz et al., and orange bars data from Mitrakou et al. The values shown represent means (±SE) measured in arterialized venous blood. Reprinted from Cryer, with the permission of the publisher.
Fasting Systems in Normal Child

Brain Metabolism (%)

Time

00

30 hr

glycogenolysis

ketogenesis

gluconeogenesis
Fasting Systems: AGA Neonate on Day 1

Brain Metabolism (%) vs. Time

- Y-axis: Brain Metabolism (%)
- X-axis: Time (0 hr to 30 hr)

The graph shows the decrease in brain metabolism over time, starting from 100% at 0 hr and decreasing to 0% at 30 hr.
Case of Neonatal Hypoglycemia:
3 wk old WM referred to Endo clinic for possible hypoglycemia

- Term pregnancy, mild maternal pre-eclampsia, BW 3.8 kg
- DOL 2 hypothermic, lethargic, BS 35 mg/dL (breast fed); repeat BS 45; discharged on DOL3
- DOL 4 at home, not nursing, lethargic in morning, seizure
- In ER BS 10 mg/dL; admitted Hosp #2, IV dextrose for 3 days, pre-feed BS 50-55 mg/dL; discharged to Endo clinic in 1-2 weeks
- 3 wk old, Endo clinic, admitted to Hosp #3
- HI documented (suspected perinatal-stress transient HI); hypoglycemia persists, Rx diazoxide; at discharge 1 week later able to fast 16 hr with BS > 70 mg/dL
- 3 mon old, trial off diazoxide: HI not resolved; probable genetic HI; diazoxide restarted (still on at age 2 yr); development 3-6 mon delayed
Categories of hypoglycemia in neonates

Transient Hypoglycemia (Day 1)
- High risk related to delayed feeding
- Mechanism: immaturities in hepatic ketogenesis and gluconeogenesis, insulin suppression until 12-24 hours

Prolonged Hypoglycemia (Day 2 up to several weeks)
- Birth asphyxia, IUGR, other peri-natal stress
- Mechanism: hyperinsulinism

Permanent Hypoglycemias presenting in neonates
- Genetic hyperinsulinism(s)
- Panhypopituitarism
- Fatty acid oxidation defects
Fasting fuels in a normal child

Plasma Fuels (mmol/l)

- FFA
- β-hydroxybutyrate
- glucose
- lactate

Length of Fast (hr)

0  12  24  36
### Metabolic fuels at time of hypoglycemia: 1\textsuperscript{st} postnatal fast in normal neonates (mmol/L, m±SD)

(Stanley, Anday, Baker, Delivoria-Papadopolous. Pediatr 1979)

<table>
<thead>
<tr>
<th></th>
<th>Glucose</th>
<th>Lactate</th>
<th>Free fatty acids</th>
<th>Total ketones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term AGA, 8 hr first postnatal fast (n=4)</td>
<td>2.1</td>
<td>3 ± 0.6(^*)</td>
<td>1.3 ± 0.23</td>
<td>0.18 ± 0.01(^*)</td>
</tr>
<tr>
<td>Older infants &amp; children</td>
<td>2.2</td>
<td>1.2 ± 0.12</td>
<td>1.55 ± 0.16</td>
<td>3.4 ± 0.27</td>
</tr>
</tbody>
</table>
Plasma Insulin in Children with Hyperinsulinism

![Graph showing plasma insulin levels in HI patients and controls.](chart.png)

- Red squares represent HI patients.
- White circles represent controls.

The graph compares plasma insulin (µU/ml) with plasma glucose (mg/dl) for both HI patients and controls.
Congenital Hyperinsulinism
Autosomal Dominant Dominant Inheritance
Congenital hyperinsulinism paradigm

1-2 days

hyperinsulinism

NH₃ / acyl-carn / AIR tests

diazoxide trial

4-7 days

PET

surgery

1-2 days

focal / diffuse Kₐ₅P

octreotide trial

(-)

(+)

GDH
GCK
SCHAD
dom Kₐ₅P
other?

4-7 days

focal / diffuse Kₐ₅P

(−)

PET

surgery

endocrinologist

geneticist

surgeon

pathologist

65%

35%

focal

local resection

diffuse

98% pancreatectomy