55 Years of Idiopathic Hypoglycemia in Infants

A historical perspective on McQuarrie’s Presidential Address to the 63rd Meeting of the American Pediatric Society.

Charles A. Stanley, MD
LWPES President 2008-09
Acknowledgements

The HI Center Team: Lori Halaby, Amanda Beattie, Sue Becker, Ashley Murray, Scott Adzick, Lisa States, Eduardo Ruchelli, etc.

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IDIOPATHIC SPONTANEOUSLY OCCURRING HYPOGLYCEMIA
IN INFANTS
Clinical Significance of Problem and Treatment

IRVINE McQUARRIE, M.D.
MINNEAPOLIS

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.†
“It’s a very rare disease—it doesn’t have a cure. It doesn’t even have a spokesperson.”
Fig. 2—Genetic factor in the syndrome of idiopathic spontaneous hypoglycemia. Family A, pedigree of the R. family. Family B, pedigree of the W. family ([J. G., B. G., J. W., and P. W.].

McQuarrrie 1954
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.
McQuarrie’s Hypoglycemia Series

The relative incidence of the various causes of spontaneously occurring hypoglycemia in one group of children is indicated by a hasty survey of patients admitted to the pediatric service of the University of Minnesota Hospitals (130-bed capacity) during the past 12 years. This showed them to be distributed on the basis of established diagnosis as follows:

1. Adrenal insufficiency.................................................. 6
2. Panhypopituitarism (pituitary dwarf)..............................1
3. Glycogen-storage disease of hepatic type (von Gierke).........3
4. Hypothyroidism (cretin).............................................1
5. Solitary pancreatic beta-cell tumor.................................1
6. Congenital galactosemia (hypoglucosemia).......................1
7. Infants of diabetic mothers.........................................2
8. Persistent spontaneous hypoglycemia, cause undetermined..... .25

Total

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McQuarrie 1954
Idiopathic Hypoglycemia: Concerns in 1953

1. Irreparable brain damage
2. Delayed diagnosis
3. Inadequate (early) therapy
4. Etiology
5. Genetic?
Idiopathic Hypoglycemia: Concerns in 1953

4. Etiology
Fig. 1.—Schematic representation of balance between hypoglycemic and hyperglycemic factors affecting carbohydrate metabolism.
Hypoglycemia induced by protein feeding, especially leucine.
Fig 2.—A schematic representation of the clinical impression of the age distribution of the various types of idiopathic hypoglycemia. Note the approximate logarithmic time scale. Comparison with Figure 1 suggests that the "leucine-sensitive," "persistent," "intractable," "familial" and some of the "unknown" categories of idiopathic hypoglycemia represent hyperinsulinism. (From Cornblath and Schwartz, p. 195.13)
Fig. 8. Fasting plasma insulin concentrations in various groups of subjects. The subject with plasma insulin concentration greater than 1,500 μU per ml had an islet cell adenocarcinoma with widespread metastases (patient of Dr. J. Field).
Hyperinsulinism in Infants and Children: Diagnosis and Therapy*

CHARLES A. STANLEY, M.D., AND LESTER BAKER, M.D.

Division of Endocrinology, Children’s Hospital of Philadelphia, and the Department of Pediatrics, University of Pennsylvania School of Medicine

Adv Pediatr 1976
Fig. 5.—Epinephrine tests of patients in first series for glycogen stores in liver and for glycogenolytic function. Blood-glucose curves show normal response.
Diagnosis of Hyperinsulinism: Inappropriate Glycemic Response to Glucagon
Neonatal Hypoglycemia at CHOP 1998-2002 (156 cases)

Hyperinsulinism 77%
- Surgical cases 34%
- Diazoxide responsive 17%
- Perinatal-stress 26%

ß-Oxidation defects & Hypopituitarism 19%

Glycogenoses 4%
Idiopathic Hypoglycemia: Concerns in 1953

1. Irreparable brain damage

2. Delayed diagnosis

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5. Genetic?
Idiopathic Hypoglycemia: Concerns in 1953

1. Irreparable brain damage
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**Idiopathic Hypoglycemia (1953)**

= 

**Congenital Hyperinsulinism (2009)**

**Synonyms:**
- Protein sensitive hypoglycemia
- Leucine sensitive hypoglycemia
- Nesidioblastosis
Fig 8.—A small pancreatic duct is surrounded by large numbers of cells shown in separate sections to be insulin-containing. This unusual finding in a pancreas with nesidioblastosis suggests the continued development of beta cells from ductal epithelium, the normal embryologic pathway. Note normal islet at top (arrow). Hematoxylin and eosin; ×200.
Fig 7. - Pinacyanole metachromasia demonstrates insulin-containing beta cells scattered singly (vertical arrow) and in small clusters (horizontal arrows) among pancreatic acinar tissue; ×400.
Pathology of Diffuse HI

Outcome: Variable
1/3: Diabetes mellitus
1/3: Hypoglycemia
1/3: controlled

Jacques Rahier 1989
Mariko Suchi 2003
Congenital Hyperinsulinism: Genes

**Glucose**

- **GK**
- **ATP**

**Insulin**

- **SUR1 & KIR6.2**
- **K\text{ATP} channel**

**Pyruvate**

- **MCT1**

**Mechanism unclear:**
- **SCHAD**
- **HNF4α**
- **UCP2**

**Calcium channel**

- **Ca\text{++}**

**Depolarization**

- **K\text{+}**

- **K\text{ATP} channel**

**Amino acids**

- **Leucine**

**Somatostatin**

**Diazoxide**

**Tolbutamide**

**Glutamate**

**Pyruvate**
# Phenotypes of Congenital Hyperinsulinism

<table>
<thead>
<tr>
<th>genetics</th>
<th>Sensitivity to stimuli / inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>diazoxide</td>
</tr>
<tr>
<td>KATP rec</td>
<td>-</td>
</tr>
<tr>
<td>KATP dom</td>
<td>+</td>
</tr>
<tr>
<td>GDH dom</td>
<td>+</td>
</tr>
<tr>
<td>GCK dom</td>
<td>±</td>
</tr>
<tr>
<td>SCHAD rec</td>
<td>+</td>
</tr>
<tr>
<td>MCT1 dom</td>
<td>?</td>
</tr>
<tr>
<td>HNF4a dom</td>
<td>+</td>
</tr>
<tr>
<td>UCP2 dom</td>
<td>+</td>
</tr>
<tr>
<td>Peri-natal stress</td>
<td>-</td>
</tr>
</tbody>
</table>
Idiopathic Hypoglycemia: Concerns in 1953

1. Irreparable brain damage
2. Delayed diagnosis
3. Inadequate (early) therapy
4. Etiology
5. Genetic?
Idiopathic Hypoglycemia: Concerns in 1953

1. Irreparable brain damage
Table 1. Summary of Published Reports of Developmental Delays in Children With HI Over the Past 25 Years

<table>
<thead>
<tr>
<th>Researcher</th>
<th>Sample Size</th>
<th>Percentage of HI Patients With Developmental Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanley and Baker, 1976</td>
<td>22</td>
<td>36</td>
</tr>
<tr>
<td>Landau et al., 1982</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>Thomas et al., 1988</td>
<td>165</td>
<td>7</td>
</tr>
<tr>
<td>Horev et al., 1991</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Spitz et al., 1992</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Dacou-Voutetakis et al., 1998</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Mahachoklertwattana,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suprasongsin, Teeraratkul, and Preeyasombat, 2000</td>
<td>10</td>
<td>70</td>
</tr>
<tr>
<td>Menni et al., 2001</td>
<td>90</td>
<td>26</td>
</tr>
<tr>
<td>Jack et al., 2003</td>
<td>55</td>
<td>44</td>
</tr>
</tbody>
</table>
Idiopathic Hypoglycemia: Concerns in 1953

1. Irreparable brain damage
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5. Genetic?
Idiopathic Hypoglycemia: Concerns in 1953

2. Delayed diagnosis

3. Inadequate (early) therapy
Reasons for Continued Poor Outcomes in Congenital Hyperinsulinism

1. Delayed Diagnosis
   - Practitioners unaware of entity
   - Lack of physical stigmata*
   - Clinical signs vague/overlooked*
   - Seizures mis-attributed to epilepsy*
   - Confusion about significance of hypoglycemia*
   - Confusion about blood sugar criteria*

2. Inadequate (early) Management*

McQuarrrie 1954
Fig 3. — Birth weight related to gestational age in 25 infants on whom data are available with onset of hyperinsulinism before 1 year of age.
Conclusions. The fact that a first nonfebrile seizure occurred in the absence of any suggestive history or symptoms in a child who is older than age 6 months and has returned to baseline has not been shown to be sufficient reason to perform routine laboratory testing in the child with a first nonfebrile seizure.

Recommendations. • Laboratory tests should be ordered based on individual clinical circumstances that include suggestive historic or clinical findings such as vomiting, diarrhea, dehydration, or failure to return to baseline alertness.12,14,15,20 (Option)
Hyperinsulinism - Hyperammonemia Syndrome
Glutamate Dehydrogenase Arg269Cys mutation

plasma ammonia (µM) 23 78 31 104 18 96

Exon 7 heteroduplexes

Thanks to Courtney Macmullen, Andrea Kelly
Hypoglycemia in Sick Children: Is it normal?

Method: Study of incidence of hypoglycemia in Boston Children’s emergency room for 1 yr (using central lab-connected beeper and one dedicated Fellow 24-7-52). A total of ~10,000 children had a BS tested.

Conclusions:
1. Incidence of hypoglycemia in sick children is very rare (~0.5%).
2. Hypoglycemia in sick children usually denotes some underlying disorder (~50%).

*Data kindly shared by David Weinstein
Use of lower glucose standards in newborns vs older children/adults

Why?

– Concern that neonatal hypoglycemia is so common it can’t be prevented.
– Concern about medico-legal liability if standards not kept low.
– Presumption that asymptomatic hypoglycemia is benign.
– etc., etc.

Consequence: Hypoglycemia goes unrecognized in the nursery in a third of neonates with severe, uncontrollable hyperinsulinism who require pancreatectomy.
Frequency of plasma glucose < 50 mg/dL in neonates


<table>
<thead>
<tr>
<th></th>
<th>Term AGA</th>
<th>All Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 1st 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>
Perinatal “Stress HI”

- Associated with IUGR, birth asphyxia, toxemia
- Glucose requirement up to 20-30 mg/kg/min
- Duration a few days up to 3+ months
- No benefit from glucocorticoids
- Responds well to diazoxide Rx
- Mechanism unknown, but may be very common (10% of SGA)

Collins & Leonard, Lancet 1984; ADC 1990
Francis Hoe, J Pediatr 2006
Management

27 infants with HI beyond 1 week old (81% males)

<table>
<thead>
<tr>
<th>Frequent feeds</th>
<th>19%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazoxide (5-15 mg/kg/d)*</td>
<td>74%</td>
</tr>
<tr>
<td>Continuous feeds</td>
<td>7%</td>
</tr>
</tbody>
</table>

* 20/22 diazoxide responsive

Francis Hoe, J Pediatr 2006
Idiopathic Hypoglycemia: Concerns in 1953

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Idiopathic Hypoglycemia: Concerns in 1953

3. Inadequate (early) therapy
Fig. 13.—Corticotropin (ACTH) therapy chart in case of J. W. (text).
Diazoxide for Hyperinsulinism

PRELIMINARY REPORT

Drug Therapy in Leucine-Sensitive Hypoglycemia

By Allan Drash and Frederick Wolff
Fig 10.—Hospital course of 4.5-month-old male infant with hyperinsulinism due to an islet cell adenoma.
Focal vs Diffuse Disease in HI Infants Requiring Surgery

Thornton, Adzick, Stanley 2002
PET Scan Alone

PET & CT Scans Combined

PET Scan Alone

Otonkoski 2001
Hardy 2007
Pre-op Diagnosis of Focal HI

Mutation analysis
(single paternal ABCC8/KCNJ11 recessive mutation)
Sensitivity 96%, Specificity 92%

F-DOPA PET
Diagnosis of focal HI:
Sensitivity 88%, Specificity 100%
Location of focal lesion:
Accuracy 100%
Outcomes for Focal HI: CHOP 12/04-12/08

Focal Cases = 56 / 102 (55%)

Surgical Outcomes:
   Cured 51 (94%)
   Hypoglycemic 3 (6%)

Location of Lesions
   Head  24 (43%)
   Head/Body  8 (14%)
   Body  10 (18%)
   Body/Tail  3 (5%)
   Tail  11 (20%)

Roux-en-Y  15 (47% of the 32 in head or body areas)
HI Treatment Options

Medical:
- Diazoxide
- Octreotide
- Continuous feedings

Surgery
- Diffuse: near-total pancreatectomy
- Focal: cure by excision
FIGURE 2. Exendin-(9–39)-normalized fasting blood glucose levels in SUR-1−/− mice. Blood glucose levels were determined after a 12–16-h fast on day 7. White bar, vehicle-treated wild-type littermates (n = 13); hatched bar, exendin-(9–39)-treated wild-type littermates (n = 10); black bar, vehicle-treated SUR-1−/− mice (n = 11); gray bar, exendin-(9–39)-treated SUR-1−/− mice (n = 11).
IDIOPATHIC SPONTANEOUSLY OCCURRING HYPOGLYCEMIA IN INFANTS

Clinical Significance of Problem and Treatment

IRVINE McQUARRIE, M.D.
MINNEAPOLIS

[Genetic diagram]

- Clinical Disease: Hypoglycemia
- Abnormal Laboratory Findings
- Normal Laboratory Findings
- Not Examined, Reported as Normal
Hakonarson, Macmullen 2008

10q21.2-q22.1

1. Irreparable brain damage  C-
2. Delayed diagnosis  C-
3. Inadequate (early) therapy  C+
4. Etiology  A-
5. Genetic?  B+
Future of Idiopathic Hypoglycemia (Hyperinsulinism)

1. New drugs needed (e.g. Exendin-(9-39))

2. More genetic loci to find: McQuarrie’s cases

3. Etiology of peri-natal stress HI to discover

4. Earlier recognition and treatment still needed
end
Idiopathic Hypoglycemia: Concerns in 1953

1. Irreparable brain damage
2. Delayed diagnosis
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5. Genetic?
<table>
<thead>
<tr>
<th>CAUSE</th>
<th>NO. OF CHILDREN</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>ALL AGES</td>
<td>ONSET &lt;1 YEAR</td>
<td></td>
</tr>
<tr>
<td>Hyperinsulinism</td>
<td>29</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>(with hypopituitarism)</td>
<td>(2)</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Ketotic hypoglycemia</td>
<td>50</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Hepatic enzyme deficiencies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose-6-phosphatase</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Amylo-1,6-glucosidase</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Fructose-1,6-diphosphatase</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Defective ketogenesis</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classification uncertain</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>98</strong></td>
<td><strong>47</strong></td>
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</table>
Table 3. Developmental Outcomes in 68 Children With HI

<table>
<thead>
<tr>
<th></th>
<th>SIB-R Standard Score Classification</th>
<th>Hypoglycemia Questionnaire</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Average and Above Average (%)</td>
<td>Low and Low Average (%)</td>
</tr>
<tr>
<td>Overall</td>
<td>69</td>
<td>15</td>
</tr>
<tr>
<td>Group A (surgical HI)</td>
<td>68</td>
<td>9</td>
</tr>
<tr>
<td>Group B (medical HI)</td>
<td>73</td>
<td>23</td>
</tr>
<tr>
<td>Group C (transient HI)</td>
<td>57</td>
<td>14</td>
</tr>
</tbody>
</table>

*Versus Group B, p < .05.
Fig 12. — Therapeutic response to intravenous diazoxide during constant infusion of 15% glucose solution in a boy age 11 years and 4 months with hyperinsulinism due to an islet cell adenoma.