History of Hyperinsulinism (HI) in Pediatrics and Overview of Diagnostic/Therapeutic Algorithm

Charles A. Stanley, MD
CHOP HI Center
Discovery of Hypoglycemia
January, 1922
(? by J.B. Collip)
“...My seemingly impulsive decision to (choose this title) was the direct result of my seeing the seventh young child....who had suffered irreparable brain damage from severe hypoglycemia....four were examples of severe spontaneous hypoglycemia in infants who were victims of delayed diagnosis and inadequate early therapy....”
Familial hypoglycemia

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.).

Fig. 3.—Photograph of J. G., aged 6 years, and B. G., aged 15 months. Two years after beginning of corticotropin therapy. Pancreatic resection scars visible.

Hexokinase 1 Mutations in McQuarrie’s Hyperinsulinism W Family

49 genes – 8.3 Mb region

63,950,212 (cent) 59,453,212 (tel)

63,950,212 (cent) 72,318,547 (tel)

49 genes – 8.3 Mb region
Idiopathic Hypoglycemia of Infancy: McQuarrie’s Findings

1. Possibly genetic?

2. Irreparable brain damage
   a) Delayed diagnosis
   b) Inadequate therapy

1. Limited treatment options
   (pancreatectomy / glucocorticoids)
“…..this abnormal relationship between amino acids and glucose metabolism has not been previously described, and will be of great interest ….to the clinician, but also the biochemist and physiologist investigating carbohydrate and protein metabolism……”
Discovery of Hyperinsulinemia in Leucine Sensitive Idiopathic Hypoglycemia of Infancy (Berson & Yalow J. Clin. Invest. 1960)

N.B.: not always clearly elevated!
Diazoxide for Treatment of Hyperinsulinism
(Drash & Wolff 1964)

Metabolism
Clinical and Experimental

VOL. XIII, NO. 6
JUNE, 1964

PRELIMINARY REPORT

Drug Therapy in Leucine-Sensitive Hypoglycemia

By Allan Drash and Frederick Wolff
“Idiopathic Hypoglycemia” becomes “Congenital Hyperinsulinism” (Haymond & Pagliara; Stanley & Baker; Aynsley-Greene)

Criteria for Clinical Diagnosis Hyperinsulinism:

1. Hyper-Insulinemia
2. Hypo-Ketonemia
3. Hypo-FFA-emia
4. Hyper-Glycemic response to Glucagon
Realization that Hyperinsulinism is not a Disorder of Embryogenesis ("Nesidioblastosis")
(Jaffe R, Hashida Y, Yunis EJ. Lab Invest. 1980

Recognition of Two Types of Hyperinsulinism: Diffuse and Focal
(Brunelle, Fekete, Saudubray, et al 1989)
Development of Centers of Excellence for HI

• France
• England (2)
• Israel
• USA (2)
• Germany
• Australia, China, etc.......
Congenital HI is Genetic: Recessive or Dominant Inheritance
The Genetic Era of Hyperinsulinism begins with Discovery of Sulfonylurea Receptor Channel Mutations
(Bryan, Aguilar-Bryan, Thomas, Gagel, Glaser, Permutt, Stanley, Thornton, etc.)

1995
### Phenotypes of Congenital Hyperinsulinism

<table>
<thead>
<tr>
<th>gene</th>
<th>genetics</th>
<th>Sensitivity to stimuli / inhibitors</th>
<th>diazoxide</th>
<th>protein</th>
<th>leucine</th>
<th>calcium</th>
<th>exercise</th>
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<tr>
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<td>?</td>
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<tr>
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<tr>
<td>Peri-natal stress</td>
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Focal HI

Genetic cause - two hit mechanism:
1) Paternal mutation found in all tissues
2) LOH of maternal allele on 11p including KATP genes and growth regulatory genes

Result: Uncontrolled islet cell proliferation forming a focal lesion which constitutively secretes insulin due to a knock out paternal mutation
Parental Genotyping
Predicting Focal-HI

<table>
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<tr>
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<th>Focal-HI</th>
<th>Diffuse-HI</th>
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<tbody>
<tr>
<td>Single recessive KATP mutation</td>
<td>144</td>
<td>9</td>
</tr>
<tr>
<td>No single recessive KATP mutation</td>
<td>4</td>
<td>95</td>
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</table>

A single heterozygous recessive mutation accurately predicts focal-HI:

- Sensitivity: 97%
- Specificity: 91%

When paternal inheritance is confirmed:

- Sensitivity: 97%
- Specificity: 93%
Fluoro-DOPA PET Imaging for focal HI

Original Article
Noninvasive Diagnosis of Focal Hyperinsulinism of Infancy With $^{18}$F-DOPA Positron Emission Tomography

Timo Otonkoski, Kirsti Näntö-Salonen, Marko Seppänen, Riitta Veijola, Hanna Huopio, Khalid Hussain, Päivi Tapanainen, Olli Eskola, Riitta Parkkola, Klas Ekström, Yves Guiot, Jacques Rahier, Markku Laakso, Risto Rintala, Pirjo Nuutila, and Heikki Minn
$^{18}$F-DOPA PET scan localization of focal adenomatosis lesion, 5 wk old neonate
This shows a large lesion in the body of the pancreas. Unfortunately, the vast majority of lesions were smaller than this and were very challenging to identify. I learned that although focal lesions maintain a lobular structure similar to that of the normal pancreas, subtle visual clues (ranging from a slightly reddish-brown color to a marble-like appearance) permitted visual detection of the lesion intraoperatively by the surgeon (NSA) in 24 of the 38 cases (including 18 of the last 23 cases). Accurate preoperative localization studies greatly facilitated the visual search for a focal lesion. In some cases the lesion felt firmer than the surrounding normal pancreas.

Need for pre-op diagnosis and localization of Focal HI
Post-Surgery Outcomes of CHOP Focal vs Diffuse HI

Outcomes of Focal Patients (55 cases)

- 95% Cured/No Meds
- 5% Not Cured

Outcomes of Diffuse Patients (43 cases)

- 47% Controlled
- 37% Required Medical Therapy for Hypoglycemia
- 16% Required Insulin Therapy for Diabetes

Location of Focal Lesions

- Head/Body 8 (15%)
- Tail 11 (20%)
- Tail/Body 3 (5%)
- Body 10 (18%)
- Head 23 (42%)
New Guidelines for Hypoglycemia Disorders in Neonates, Infants, and Children from the PES (free on-line!!)

Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children

Paul S. Thornton, MB, BCh1, Charles A. Stanley, MD2, Diva D. De Leon, MD, MSCE2, Deborah Harris, PhD3, Morey W. Haymond, MD4, Khalid Hussain, MD, MPH5, Lynne L. Levitsky, MD6, Mohammad H. Murad, MD, MPH7, Paul J. Rozance, MD8, Rebecca A. Simmons, MD9, Mark A. Sperling, MBBS10, David A. Weinstein, MD, MMSc11, Neil H. White, MD12, and Joseph I. Woflsdorf, MB, BCh13

Re-Evaluating “Transitional Neonatal Hypoglycemia”: Mechanism and Implications for Management

Charles A. Stanley, MD1, Paul J. Rozance, MD2, Paul S. Thornton, MB, BCh3, Diva D. De Leon, MD4, Deborah Harris, PhD5, Morey W. Haymond, MD6, Khalid Hussain, MD, MSCE7, Lynne L. Levitsky, MD8, Mohammad H. Murad, MD, MPH9, Rebecca A. Simmons, MD10, Mark A. Sperling, MBBS11, David A. Weinstein, MD12, Neil H. White, MD12, and Joseph I. Woflsdorf, MB, BCh13


HI Treatment Options 1985-now

**Medical:**
- Diazoxide
- Octreotide
- Continuous tube feedings

**Surgery**
- Diffuse: near-total pancreatectomy
- Focal: cure by excision
Lizard Spit for HI?

Exendin-(9-39) = GLP-1 antagonist
Exendin-(9-39) corrects fasting hypoglycemia in \textit{SUR1}\textsuperscript{−/−} mice.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{exendin.png}
\caption{Blood Glucose (mg/dL) levels for different groups.}
\end{figure}

Futuristic HI Treatments

- Long-acting Octreotide (Paris, Germany)
- GLP-1 receptor antagonist (Philly)
- Sirolimus (London)
- ...at least 3 other potential agents in the pre-clinical pipeline (...that I know about!):
  - IR antibody (XOMA)
  - Soluble Glucagon for pumps (XERIS)
CHI and the Future of HI

1. Advocacy (improved detection & early treatment, barriers to treatment, research funds…)

2. Networking (family support, education, other rare disease groups, HI patient registry…)

3. Fund-raising (research, training, patient assistance, public awareness…)

4. etc., etc., etc......
“It’s a very rare disease—it doesn’t have a cure.
It doesn’t even have a spokesperson.”
Congenital Hyperinsulinism: Genes

- glucose
- pyruvate
- MCT1
- mechanism unclear: SCHAD, HNF4a, UCP2
- HK1, PGM1
- GDH
- glutamate
- amino acids
- leucine
- ATP
- Insulin
- Ca^{++}
- calcium channel
- somatostatin
- diazoxide
- tolbutamide
- depolarization
- K^+_ATP channel
- SUR1 & KIR6.2
- ATP
- depolarization
Mutations in 705 Children with Congenital HI (1997-2014)

Diazoxide-Responsive
(219)

- 1 dom UCP2
- 1 dom HNF4A
- 1 dom HNF1A
- 2 rec SCHAD
- zero mutations (dom mosaic KATP/GLUD1)

Diazoxide-Unresponsive
(434)

- diffuse (1 dom KATP)
- diffuse (2 rec KATP)
- focal (1 rec KATP) (no surgery)
- focal (1 rec KATP) (no surgery)
- (mostly KATP mutations)
- zero mutations (dom mosaic KATP/GLUD1)

1 dom KATP
1 dom GLUD1
1 dom UCP2
1 dom HNF4A
2 rec SCHAD
1 dom HNF1A
1 dom GLUD1
1 dom KATP
zero mutations (dom mosaic KATP/GLUD1)