Congenital Hyperinsulinism Family Conference
September 29-30, 2015
Hospital Sant Joan de Déu
Barcelona, Spain

Tuesday, September 29, 2015

8:00 a.m.  Registration

8:30 a.m.  Welcome and Introductions
Julie Raskin, Congenital Hyperinsulinism International (Conference Moderator)
Dr. Paula Casano, Hospital Sant Joan De Déu

8:40 a.m.  The Historical Perspective: How Basic Scientific Understanding has Led to Improvements in Hyperinsulinism Treatment
Joseph Bryan, PhD, Pacific Northwest Diabetes Research Institute
Charles Stanley, MD, Children’s Hospital of Philadelphia

9:25 a.m.  The Genetics of Hyperinsulinism
Sian Ellard, PhD FRCPA, Head of Molecular Genetics, Royal Devon & Exeter NHS Foundation Trust and Professor of Human Molecular Genetics, University of Exeter Medical School

10:05 a.m.  Tools for Diagnosing Hyperinsulinism
Jean Baptiste-Arnoux, MD, Necker Hospital and Klaus Mohnike, MD, University of Magdeburg

10:35 a.m.  Break

10:55 a.m.  Current Hyperinsulinism Treatment
Diva DeLeon, MD, Children’s Hospital of Philadelphia, Khalid Hussain, MD, GOSH,

11:30 a.m.  Patients and their Families Share Triumphs and Challenges
Moderated by Sheila Bose, Patient Advocate
Confirmed Speakers: Adrienne Burton, Jessica Burton, Connie Ward, Matthew Hammond

Topics: Feeding
Historical Perspective:
How Basic Science has Improved Treatment of HI

Part 2: The Clinician’s Perspective

Charles A. Stanley, MD
Hyperinsulinism Center
Children’s Hospital of Philadelphia
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.†
Congenital Hyperinsulinism

- Most common form of hypoglycemia in children
  - >1 in 20,000 births
  - 1 in 10 SGA babies (Transient)
- Glucose requirement up to 50 mg/kg/min (10x normal)
- High risk of seizures & brain damage
- Pancreatectomy often needed
- Half of surgical cases have a curable focal lesion
- 9+ genetic loci
Congenital Hyperinsulinism: 10 Genes

- HNF1a
- HK1
- GK
- G6P
- MCT1
- Pyruvate
- SCHAD
- GDH
- Ac-CoA
- α-KG
- ATP/ADP
- UCP2
- SUR1
- K^+
- Ca^{++}
- tolbutamide
- diazoxide
- depolarization
- GLP1
- GLP1R
- Exendin-(9-39)
- Ac-Ch
- PLC
- DAG
- PK-A
- PK-C
- HNF4α
- HNF1a
- Leucine
- Glutamine
- Glutamate
- Amplification pathways?
- INS
- Epinephrine
- Somatostatin
<table>
<thead>
<tr>
<th>gene</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>-</td>
</tr>
<tr>
<td>KATP</td>
<td>dom</td>
<td>+</td>
</tr>
<tr>
<td>GDH (HI-HA)</td>
<td>dom</td>
<td>+</td>
</tr>
<tr>
<td>GCK</td>
<td>dom</td>
<td>-</td>
</tr>
<tr>
<td>SCHAD</td>
<td>rec</td>
<td>+</td>
</tr>
<tr>
<td>MCT1</td>
<td>dom</td>
<td>?</td>
</tr>
<tr>
<td>HNF4a</td>
<td>dom</td>
<td>+</td>
</tr>
<tr>
<td>UCP2</td>
<td>dom</td>
<td>+</td>
</tr>
<tr>
<td>Peri-natal stress</td>
<td>NA</td>
<td>+</td>
</tr>
</tbody>
</table>
Mutations in 705 Children with Congenital HI (1997-2014)

**Diazoxide-Unresponsive**
- 434 cases
  - Diffuse (2 rec KATP)
  - Focal (1 rec KATP, no surgery)
  - (mostly KATP mutations)
  - Diffuse (1 dom KATP)
  - Focal (1 rec KATP, GCK)
  - Zero mutations (?dom mosaic KATP/GCK)

**Diazoxide-Responsive**
- 219 cases
  - Zero mutations (?dom mosaic KATP/GLUD1)
  - 2 rec SCHAD
  - 1 dom UCP2
  - 1 dom HNF4A
  - 1 dom HNF1A
  - 1 dom GLUD1
  - 1 dom KATP
  - (mostly no mutations)
Need for pre-op diagnosis and localization of Focal HI
Focal HI

Genetic cause – “two hit” mechanism:
1) Paternal mutation (present in all cells)
2) LOH of maternal allele on 11p (no KATP genes and no growth regulatory genes)

Result: Uncontrolled islet cell proliferation forming a focal lesion that continuously releases insulin due to a knock out paternal mutation in ABCC8 or KCNJ11
Parental Genotyping  
Predicting Focal-HI

<table>
<thead>
<tr>
<th></th>
<th>Focal-HI</th>
<th>Diffuse-HI</th>
</tr>
</thead>
<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>
</tr>
</tbody>
</table>

A single heterozygous recessive mutation accurately predicts focal-HI:

Sensitivity: 97%
Specificity: 91%

When paternal inheritance is confirmed:

Sensitivity: 97%
Specificity: 93%
F-DOPA PET images--Focal HI

A. Normal pancreatic tissue and focal lesion in head of kidneys.

B. Focal lesion in pancreas head and kidneys.

C. Focal lesion in pancreas head and kidneys.

D. Pancreas tail and body, liver, and kidney.
Post-Surgery Outcomes of CHOP Focal vs Diffuse HI (since 2008)

Outcomes of Focal Patients (55 cases)
- Cured/No Meds: 95%
- Not Cured: 5%

Location of Focal Lesions
- Head/Body 8 (15%)
- Tail 11 (20%)
- Tail/Body 3 (5%)
- Body 10 (18%)
- Head 23 (42%)

Outcomes of Diffuse Patients (43 cases)
- Controlled: 47%
- Required Medical Therapy for Hypoglycemia: 37%
- Required Insulin Therapy for Diabetes: 16%
HI Treatment Options 1985-now

Medical:
- Diazoxide
- Octreotide
- Continuous tube feedings

Surgery
- Diffuse: near-total pancreatectomy
- Focal: cure by excision
Futuristic HI Treatments

Long-acting Octreotide (Paris, etc.)

GLP-1 antagonist (Philly)

Sirolimus (London)

....at least 3 other potential agents in the pre-clinical pipeline (…that I know about!)
New Guidelines to Aid in Diagnosing Congenital HI from the PES (free on-line!!)

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

Charles A. Stanley, MD,1 Paul J. Roccaze, MD,2 Paul S. Thornton, MB, BCN,2 Diva D. De Leon, MD,2
Deborah Harris, PhD,1 Maryly W. Raymond, MD,1 Khalid Hussain, MD, MSC,1 Lynne L. Levintal, MD,1
Mohammed H. Murad, MD, MPH,1 Rebecca A. Simmon, MD,1 Mark A. Spanger, MBBS3
David A. Weinstein, MD,1 Neil H. White, MD,1 and Joseph I. Wolfsdorf, MB, BCN1

A Committee of the Pediatric Endocrine Society was recently formed to develop guidelines for evaluation and management of hypoglycemia in neonates, infants, and children. To aid in formulating recommendations for neonates requiring diagnosis and treatment during the first days of life for disorders causing severe and persistent hypoglycemia, it has long been known that plasma glucose concentrations are lower in the first 1 to 3 days of life in normal newborns than at a later age. Until the 1990s it was appreciated that hypoglycemia in neonates could sometimes be symptomatic and, as its infants and children, cause serious or permanent brain damage. Thus, studies in laboratory animals have demonstrated postnatal developmental changes in liver glycogen, glucose transport, and glucokinase and glucokinase activity levels. It is unclear how such changes adequately explain transitional neonatal hypoglycemia in human newborns or if other mechanisms may be involved. A National Institutes of Health conference outlined many of the “paradigm shifts” about neonatal hypoglycemia and lamented the lack of a rational basis for defining hypoglycemia in neonates.1 For this re-evaluation of transitional neonatal hypoglycemia in normal newborns, we used the strategy routinely employed by pediatric endocrinologists for evaluation of hypoglycemia in older infants and children. Thus, based on an examination of the major metabolic fuel and hormone responses to hypoglycemia, it makes possible to focus on mean responses as being most likely representative of normal newborns, recognizing the possibility of heterogeneity, particularly with regard to perturbation stressors and feeding practices. We found that transitional neonatal hypoglycemia closely resembles known genetic forms of congenital hyperinsulinism, which cause a lowering of the plasma glucolice through suppression of insulin secretion. This conclusion is based on strong evidence supported by two or more independent reports and provides a novel perspective on both the diagnosis and management of hypoglycemia in the first several days after birth.

Patterns of Plasma Glucose Concentrations in Normal Newborns During the First Days of Life

Prior to birth, fetal fuel metabolism is based primarily on utilization of glucose, which is supplied from maternal placenta glucose whose levels are regulated by maternal insulin secretion.2 The fetal brain is exposed to diluting glucose concentrations only slightly below those of maternal plasma; with normal maternal glucose concentrations of 70-90 mg/dL (3.9-5.0 mmol/L), mean fetal-placental plasma glucose difference at term is only 9 mg/dL (0.5 mmol/L).3 Fetal insulin is expensive to fetal plasma glucose concentrations, but fetal glucose concentrations are determined primarily by maternal glucose concentration wherein fetal insulin primarily functions to regulate growth.4

Immediately following birth, in normal newborns, the mean plasma glucose concentrations drop by 20-30 mg/dL.


end
## 185 KATP Channel Mutations in ABCC8 & KCNJ11 Genes

### Type of Mutation

<table>
<thead>
<tr>
<th>Type of Mutation</th>
<th>Mode of Inheritance</th>
<th>Number in ABCC8</th>
<th>Number in KCNJ11</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Missense</strong></td>
<td>Recessive</td>
<td>62</td>
<td>17</td>
<td>Diazoxide Unresponsive</td>
</tr>
<tr>
<td></td>
<td>Dominant</td>
<td>12</td>
<td>0</td>
<td>Diazoxide Unresponsive*</td>
</tr>
<tr>
<td><strong>Nonsense</strong></td>
<td>Recessive</td>
<td>44</td>
<td>1</td>
<td>Diazoxide Unresponsive</td>
</tr>
<tr>
<td><strong>Splicing</strong></td>
<td>Recessive</td>
<td>24</td>
<td>0</td>
<td>Diazoxide Unresponsive</td>
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<tr>
<td><strong>Frame-shift</strong></td>
<td>Recessive</td>
<td>23</td>
<td>0</td>
<td>Diazoxide Unresponsive</td>
</tr>
<tr>
<td><strong>Large Duplication</strong></td>
<td>Recessive</td>
<td>1</td>
<td>0</td>
<td>Diazoxide Unresponsive</td>
</tr>
</tbody>
</table>
CHI Children seen at
The Children’s Hospital of Philadelphia between 1997-2014

Diazoxide Responsive
n = 219 (34%)

Diazoxide Unresponsive
n = 434 (66%)

HI Panel ‡
N = 653 (93%)

SURGICAL
n = 407 (94%)

FOCAL HI
n = 201 (49%)

DIFFUSE HI
n = 186 (76%)

“ATYPICAL”
n = 13 (3%)

NON-SURGICAL
n = 27 (6%)

‡Tier 1 = ABCC8, KCNJ11, GCK, GLUD1
KATP HI mutations:
Recessive or Dominant Inheritance

delPhe1388 homozygous

p.delSer1387 heterozygous
1-RecKATP(focal)
2-RecKATP(diffuse)
1-DomKATP(diffuse)
zero mutations(mosaicKATPdom)
1-DomGCK(diffuse)
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