18F-DOPA in the evaluation of Congenital Hyperinsulinism

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Congenital Hyperinsulinism (HI)

- First described in 1954 by MacQuarrie
- Idiopathic hypoglycemia of infancy
- Hyperinsulinemic hypoglycemia
- Characterized by dysregulated pancreatic β cell insulin secretion that results in persistent mild to severe hypoglycemia.
HI

- Heterogeneous disorder
  - Clinically - mild to severe
  - Genetically - 5 different genes associated
  - Histopathology – focal vs. diffuse
- Most common cause of *persistent* hypoglycemia in infants.
- Frequency
  - 1/30,000 to 1/50,000 live births
  - 1/2500 live births in Arabian peninsula
Clinical Px

- Lethargy, seizures, poor feeding, LOC
- Require glucose infusion rates as high as 20-30mg/kg/min to control blood glucose levels.
- At risk for seizures, permanent brain damage and mental retardation.
- Mental retardation in 40% with delayed Dx.
- The goal of treatment is prevention of brain damage.
DDX hypoglycemia

- Infant of Diabetic mother
- Perinatal stress, asphyxia
- IUGR/SGA
- Toxemia (terbutaline)
- Beckwith-Wiedemann Syndrome
- Hypopituitarism
- Antiinsulin and insulin-receptor stimulating Ab
- Insulinoma
- Congenital disorders of glycosylation
Neonatal Hypoglycemia at CHOP
1998-2002 (156 cases)

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

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Hyperinsulinism Dx

- LGA
- Increased glucose utilization
- During hypoglycemia (glu < 50mg/dl)
  - Hyperinsulinemia
  - Hypofattyacidemia
  - Hypoketonemia
  - Glycemic response to glucagon
HI Genetic mutations

- **KATP** – HI
  - ABCC8/SUR-1 (sulfonylurea receptor 1) and/or
  - KCNJ11/Kir6.2 (potassium inward rectifying channel)
    - Recessive
    - LOH & paternal mutation
    - Dominant
- **Dominant Glucokinase**
- **Dominant Glutamate dehydrogenase**
- **Recessive SCHAD** (Short-chain 3 hydroxyacyl-CoA dehydrogenase)
- **MCT** (exercise induced)
KATP HI

- SUR-1 and Kir6.2 combine to form the beta cell plasma membrane KATP channel.
- Most common form of HI
- Most severe form of HI
- Focal and diffuse histology
- 75% of surgically treated patients
Pancreatic Beta cell

Diazoxide opens channel. (not if defective)

Octreotide inhibits Calcium voltage channel by hyperpolarization.

**Glucose Glutamate**

**ATP-sensitive K+ channel**

- Mutations inactivate KATP channel, causing closure of the channel → membrane depolarization → calcium influx → release of insulin.

- Diazoxide opens channel.
- Octreotide inhibits Calcium voltage channel by hyperpolarization.

- Glucose → GK → ATP/ADP/P → Ca2+ → depolarization → Voltage dep Ca2+ channel

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

Localized adenomatosis of Beta cells

Linda Ernst, MD
Diffuse HI

Genetic cause:
1) Paternal mutation that may or may not be found in all tissues
2) Maternal mutation that may or may not be found in all tissues

Diffuse Islet cell hyperplasia
Prevalence of Focal HI
CHOP

166 pancreatectomy patients, 12/98 – 1/07

86 Focal
3 Focal/Redo
77 Diffuse

Focal 54%
Diffuse 46%
Medical therapy

- Controlled diazoxide (PO)
- Controlled octreotide (SQ)
- Enteral feedings
- Nifedipine
- IV glucagon
Surgical Management

- No response to medical therapy
- Cannot maintain glucose > 70mg/dl of IV
  - Failed diazoxide (15mg/kg/d) for 5 days
  - Failed Octreotide 15-20mcg/kg/d for 2-3 days
  - Continuous IV Feeds of 6-8mg dextrose/kg/min
Congenital Hyperinsulinism Paradigm 2007

- hypoglycemia → fasting test → hyperinsulinism
  - NH₃ / acyl-carn / AIR tests / mol diag
  - diazoxide trial (-) → GDH, GCK, SCHAD, dom K\textsubscript{ATP}, MCT-1, other?
  - octreotide trial (-) → ¹⁸F-DOPA PET
  - surgery
    - focal
      - 60% focal resection
      - 40% diffuse
    - diffuse 98% pancreatectomy

endocrinologist

nuclear medicine physician

geneticist

surgeon

pathologist
Diffuse HI Surgery

- Subtotal pancreatectomy >97%
- Biopsy 3 regions of pancreas, head, neck and tail, for signs of diffuse disease on frozen section.
- Gastrostomy
Surgical outcome

- Subtotal pancreatectomy
  - 1/3 cure
  - 1/3 hypoglycemia, controlled with med
  - 1/3 diabetes
- Prevent neurologic damage
Focal lesions

- Limited focal resection
- Confirm focal Beta cell adenomatosis
- Continuous frozen section until normal islet cells found
- May need Roux-en-Y if lesion is in pancreatic head
- Rise in glucose immediately after removal, then euglycemic – no medications
Partial pancreatectomy

- Cure hypoglycemia
- Decrease risk of diabetes
- Decrease risk of pancreatic insufficiency
- Prevent neurologic damage
18F L-fluoro-dihydroxyphenylalanine

- 88% accurate in diagnosing focal disease
- 100% accurate in localizing focal lesions
Mechanism

- 18 FDOPA is taken up in pancreatic Beta cells and decarboxylated to dopamine by aromatic amino acid decarboxylase (AADC) system and stored in vesicles.
- 18F DOPA PET identifies increased islet cell activity.
Normal distribution

- Pancreas
- Liver
- Metaphyses/growth plates
- Gall bladder
- Duodenum
- CBD
# Review of Literature

<table>
<thead>
<tr>
<th>Author Journal</th>
<th>Country</th>
<th>N</th>
<th>Accuracy focal dx</th>
<th>Accuracy localization</th>
<th>imaging</th>
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<td>Otonkoski et al 2006</td>
<td>Finland</td>
<td>14 F 9 D 4DS</td>
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<td>100%</td>
<td>MRI</td>
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<td>Ribeiro, et al 2005</td>
<td>Paris France</td>
<td>15 F 10D 4DS</td>
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<td>Hardy, et al 2006</td>
<td>CHOP/UPENN</td>
<td>24 F 11 F 12 DS</td>
<td>96%</td>
<td>100%</td>
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<td>Barthlen et al 2007</td>
<td>Germany</td>
<td>10F</td>
<td>90% 1 atypical</td>
<td>100%</td>
<td>PET/CT</td>
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### Review of Literature

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<thead>
<tr>
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<th>CHOP/UPENN</th>
<th>N=50</th>
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<td>18</td>
<td>0</td>
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<tr>
<td>Diffuse</td>
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**Histology**

- Accurary focal vs diffuse 88% (44/50)
- Sensitivity of detecting focal lesion 75%
- PPV 100%
- 2 atypical
6 focal lesions

- 5 Small (.6mm +/- .2mm), (1.3 +/- 4.2mm)
  - Thin lesion
  - In tail adjacent to kidney
- 1 large 80-90% pancreas
Review of Literature

- 21/24 pts. (88%) Path confirmed PET
- SUV head>rest, focal significant 1.44 +/- 0.17
- Carbidopa (no uptake)
- Medication effects
  - Octreotide, diazoxide (unchanged)
  - Glucagon (no uptake)
- Atypical form

Prior techniques

- Pancreatic venous sampling
- Pancreatic arterial calcium stimulation test
- Accuracy up to 80%.
- CT and MRI not useful.
- General anaesthesia
- Invasive
- glucose levels need to be stable
CHOP/HUP protocol

- Patients not controlled by medication, possible focal lesion
- Controlled on medication but may have a focal lesion
- Possible regrowth or residual after pancreatectomy
- Known GK or GDH excluded
Preparation for $^{18}$FDOPA

- Medications that may interfere with uptake are discontinued.
- Diazoxide min 5 days
- Octreotide min 2 days
- Glucagon min 12 hours
- Blood glucose maintained 70 -100 mg/dl checked hourly
CHOP Protocol

- Maintenance IV fluids
- Sedation (light)
- Urinary bladder catheterization
- 3-6 MBq/kg (0.08 to 0.16 mCi/kg) IV over 1 minute
- Low dose CT for attenuation correction
- 3-D acq PET, 1 bed position, every 10 minutes for 50 minutes
- Surgery 12 to 18 hours
18F-DOPA

- Synthesized in the cyclotron at UPENN medical school
- Approved by Radiation safety committee
- FDA oversight of IND, Dr. Divgi
Evaluation

- 3D MIP
- Reconstruction
  - Sagittal
  - Axial
  - Coronal
- Image fusion
Pitfalls

- Pancreatic tail
- CBD excretion
- Increased activity head (50% of pancreatic tissue)
2 different patients

Diffuse

Focal
5yo

Insulinoma
Insulinoma

- KATP LOH
- Kauhanen et al. 10 Adult patients, 8 F, 2D
- 9 underwent surgery
- 100% accuracy Dx.
- CT 30%
- MR 40%
Proposal for

Proposal for a Standardized protocol for 18-F-DOPA-PET (PET/CT) in Congenital Hyperinsulinism

Mohnike, et al

Hormone Research *concensus paper*
2006;66 pp40-42
Conclusion

- 18F-DOPA-PET (PET/CT) has become the preferred method for differentiation between focal and diffuse Congenital Hypothyroidism (Congenital HI).
- Accurate preoperative localization allows a curative limited resection without the long-term risk of diabetes.
- A multidisciplinary team is essential.
Special thanks

Charles Stanley (Chief of Endocrinology, CHOP)
Scott Adzick (Chief of Surgery, CHOP)
Sue O’Rourke (Clinical Coordinator, CHOP)
Diego Jaramillo (Chief of Radiology, CHOP)
Chaitanya Divgi (Chief of Nuclear medicine, HUP)
Hongming Zhuang (Chief of Nuclear medicine, CHOP)
Linda Ernst (Pathology, CHOP)
Roberto Accorsi (Research Phd, CHOP)
Kevin Edwards (Head NM Technologist)
Jen Conover (PET Technologist)
Laura Wanner (HI Team)
Lori Halaby (HI Team)
Olga Hardy (HI Team)
Abass Alavi (Original IND, HUP)
72 $^{18}$F-DOPA PET scans
(December 2004 – December 2007)

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