Surgical Management of Endogenous Hyperinsulinism

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Texas Chapter of AACE
Texas Endocrine Surgical Symposium
San Antonio, Texas
August 4, 2017
Disclosures

I have nothing to disclose
History

Insulin-secreting islet cell tumor of pancreas

• 1902 Nicholls described first adenoma of pancreatic islet cells
• 1927 Wilder demonstrated the relationship between hyperinsulinism and a malignant islet cell tumor by means of bioassay of the metastasis for insulin
• 1929 Graham removed a benign functioning insulinoma producing relief of symptoms; no recurrence 10 years later
• 1935 Whipple and Franz reported 6 cases of insulinoma and established diagnostic criteria
Whipple’s Triad
(clinical features of insulinoma)

• Neuroglycopenic symptoms consistent with hypoglycemia
• Low plasma glucose measured when symptoms are present
• Relief of symptoms with administration of glucose

Symptomatic Hypoglycemia
Differential Diagnosis

- Insulinoma
- Noninsulinoma pancreatogenous hypoglycemia syndrome
- Exogenous administration of insulin or oral hypoglycemic drugs
- Insulin autoimmune hypoglycemia
- Insulin-like growth factor-mediated hypoglycemia
Causes of Hypoglycemia

• Medication or toxin related:
  Exogenous insulin (treatment of DM or factitious)
  Sulfonylureas
  Ethanol

• Post-prandial hypoglycemia
  Post-gastric resection (dumping)
  Reactive hypoglycemia

(continued)
Causes of Hypoglycemia II

- Fasting hypoglycemia
  - Diffuse hepatic dysfunction (cirrhosis, CHF)
  - Humoral tumor-associated hypoglycemia
  - Auto-immune disorders
  - Uremia
  - Insulinoma
Pancreatic Neuroendocrine Tumors

- Non-functional
- Insulinoma
- Gastrinoma
- VIPoma
- Glucagonoma
- Somatostatinoma
- Pancreatic Polypeptide?
# Nomenclature, Incidence, Location and Malignancy of Pancreatic NETs

<table>
<thead>
<tr>
<th>Name</th>
<th>Hormone</th>
<th>Cell Type</th>
<th>Incidence</th>
<th>Pancreas</th>
<th>Duodenum</th>
<th>% Malignant</th>
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</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>Insulin</td>
<td>β islet cells</td>
<td>1 / 1.25M</td>
<td>&gt;99%</td>
<td></td>
<td>5-11%</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Gastrin</td>
<td>G cells</td>
<td>1 / 2.5M</td>
<td>21-65%</td>
<td>6-35%</td>
<td>60%</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Glucagon</td>
<td>α cells</td>
<td>&lt; 1 / 5M</td>
<td>&gt;99%</td>
<td></td>
<td>&gt;70%</td>
</tr>
<tr>
<td>VIPoma</td>
<td>VIP</td>
<td>δ cells</td>
<td>&lt; 1 / 5M</td>
<td>85-90%</td>
<td>10-15%</td>
<td>50%</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Somatostatin</td>
<td>δ cells</td>
<td>&lt; 1 / 10M</td>
<td>50%</td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td>Nonfunctioning</td>
<td>Neuron-specific enolase, PP</td>
<td>F cells</td>
<td>1 / 5M</td>
<td>&gt;99%</td>
<td></td>
<td>&gt;50%</td>
</tr>
</tbody>
</table>

Pancreatic NETs

Tumor

Capsule

Normal islet
Insulinoma

- Most common functioning endocrine neoplasm of the pancreas.
- Usually small (1.0 – 1.5 cm), solitary and benign when they occur sporadically.
- Evenly distributed throughout pancreas, and essentially always intrapancreatic.

- Extrapancreatic insulinomas are extremely rare, but have been described in duodenal wall*, splenic hilum or gastrocolic ligament.

Pancreatic insulinoma:
Insulin immunostain

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https://commons.wikimedia.org/w/index.php?curid=507388
Neuroglycopenia symptoms

- Manifestations of sympathetic response to hypoglycemia (diaphoresis, tachycardia, tremor, anxiety)

- CNS effects (irritability, excitement, lethargy, hunger, blurred vision, confusion, loss of orientation, apathy, stupor, slowed thinking or responsiveness)
Clinical Recognition

- Patients often documented to have profound hypoglycemia (glucose <40 mg/dL during fasting or after exercise)
- May have profound episodic confusion or lethargy, presyncope or seizures
- Presenting symptoms are neither unique or specific, and may seem bizarre
- The diagnosis may be delayed for months or years owing to atypical presentation, poor physician awareness, and attributing clinical picture to another cause
Important Features of Clinical Presentation and Diagnostic Considerations

- Temporal relationship between neuroglycopenic symptoms and fasting, relief of symptoms after eating
- Patients often carry sugar tablets, candy bars, or need to awaken at night to eat
- Two thirds of patients with insulinoma have significant weight gain to compensate for episodic hypoglycemia
- Factitious hypoglycemia (surreptitious administration of insulin or other medications) must be excluded in all patients undergoing evaluation for insulinoma
Insulinomas

- Incidence of 0.8 to 0.9 cases/million persons/yr, avg. age is 45 yr, Female > Male predominance
- Most are sporadic, approximately 5% are associated with MEN 1, <10% malignant
- Common symptoms include confusion, diplopia, tremulousness, diaphoresis, syncope, and headache
- Diagnosed by 72 hour in-patient fast
  - 75% pts symptomatic after 24hrs, 95% at 48hrs

Typically
- glucose < 40 mg/dL
- insulin > 5 microU/mL
- C-peptide > 1.2 ng/mL
- proinsulin > 25%
- I/G > 0.3
NIPHS

• Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) is a rare syndrome characterized by endogenous hyperinsulinemic hypoglycemia that is not caused by an insulinoma
• Pancreatic specimens from such patients show beta cell hypertrophy, islets with enlarged and hyperchromatic nuclei, and increased islets budding from periductular epithelium
NIPHS (2)

- The noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) identifies a group of hyperinsulinemic hypoglycemic patients with unique clinical, diagnostic, surgical, and pathologic features.
- These patients experience predominantly postprandial hypoglycemia and have nesidioblastosis with islet cell hypertrophy, findings different from those in patients with insulinomas.
NIPHS (3)

• Formal epidemiologic studies have not been conducted for NIPHS; however, the condition appears to be rarer than insulinoma. For example, during the period from 1996 to 2004, 20 patients with NIPHS (16 male, 4 female) and 118 patients with insulinoma (51 male, 67 female) were surgically confirmed at the Mayo Clinic. [1-3]

• Although the underlying pathologic features of NIPHS and post-gastric bypass hypoglycemia are similar in most instances, post-gastric bypass hypoglycemia is considered a separate clinical entity.

Case Presentation #1

- 18 y/o female, family history of MEN 1
- Bizarre behavior, especially after awakening in morning: belligerent, inappropriate/ incomprehensible speech, sweating
- Recognition of the association of symptoms with fasting, relieved by eating
Supervised in-hospital fast: Diagnostic workup of fasting hypoglycemia

- Start IV, intravenous fluids without dextrose (1/2 NS)
- Patient may take non-caloric fluids ad lib
- Have amp D50 immediately available and pre-labeled tubes for planned timed samples
- Glucose measurement every 1-2 hours until glucose ≤ 50, then every hour
- Fast terminated when patient is profoundly hypoglycemic and symptomatic
- Final measurement of glucose, insulin, C-peptide, sulfonylurea screen
- Administer D50
Laboratory values at termination of fast

- Glucose: 24 mg/ dL (85-125)
- Insulin: 26 uIU/ mL (1.4 - 14)
- C-peptide: 5.2 ng/ mL (0.9 – 4.3)
  1716 pmol/ L (297 – 1419)
- Oral hypoglycemic screen negative
- Insulin antibodies negative
## Interpretation of Laboratory Results and Differential Diagnosis in Fasting Hypoglycemia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Glucose mg/dL</th>
<th>Insulin uU/mL</th>
<th>C-Peptide nmol/L</th>
<th>Pro-Insulin pmol/L</th>
<th>Anti-Insulin AB</th>
<th>Oral Hypoglycemic meds</th>
<th>Beta OH-butyry</th>
<th>Panc mass</th>
<th>Timing of Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>&lt;55</td>
<td>≥3</td>
<td>&gt;0.2</td>
<td>≥5</td>
<td>-</td>
<td>No</td>
<td>≤2.7</td>
<td>Yes</td>
<td>Fasting</td>
</tr>
<tr>
<td>NIPHS</td>
<td>&lt;55</td>
<td>≥3</td>
<td>&gt;0.2</td>
<td>≥5</td>
<td>-</td>
<td>No</td>
<td>≤2.7</td>
<td>No</td>
<td>Post-prandial</td>
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<tr>
<td>Surreptitious Insulin admin</td>
<td>&lt;55</td>
<td>&gt;&gt;&gt;&gt;3</td>
<td>&lt;0.2</td>
<td>&lt;5</td>
<td>-</td>
<td>No</td>
<td>≤2.7</td>
<td>No</td>
<td>After insulin admin</td>
</tr>
<tr>
<td>Oral Hypoglycemic med admin</td>
<td>&lt;55</td>
<td>≥3</td>
<td>&gt;0.2</td>
<td>≥5</td>
<td>-</td>
<td>Yes</td>
<td>≤2.7</td>
<td>No</td>
<td>After med admin</td>
</tr>
<tr>
<td>Insulin autoimmune</td>
<td>&lt;55</td>
<td>&gt;&gt;&gt;&gt;3</td>
<td>&gt;&gt;0.2</td>
<td>&gt;&gt;&gt;&gt;5</td>
<td>+</td>
<td>No</td>
<td>≤2.7</td>
<td>No</td>
<td>Fasting</td>
</tr>
<tr>
<td>IGF-mediated</td>
<td>&lt;55</td>
<td>&lt;3</td>
<td>&lt;0.2</td>
<td>&lt;5</td>
<td>-</td>
<td>No</td>
<td>≤2.7 &gt;2.7</td>
<td>No</td>
<td>Fasting</td>
</tr>
</tbody>
</table>
Radiographic Localizing Tests

- Insulinomas may be occult and difficult to localize preoperatively

- Accurate localization prior to exploration is optimal, with careful selection of appropriate tests:
  - Computed tomography/MRI
  - *Endoscopic ultrasound* (operator-dependent)
  - Arteriography (especially selective pancreatic arteriogram with calcium stimulation)
Selective Pancreatic Arteriography with Intra-arterial Calcium Gluconate

- Infusion of calcium gluconate into selectively catheterized pancreatic or hepatic arteries (gastroduodenal a., superior mesenteric a., splenic a., hepatic a.)
- Measurement of insulin secretion in separate catheter positioned in the hepatic vein

Selective Pancreatic Arteriography
Provocative Angiogram in Patient with MEN 1 and Insulinoma

Patient #9

Gluconeogenic hormone level above baseline

Time after injection (seconds)

- SMA
- SPL
- GDA
- CHA
Pancreatic Neuroendocrine Tumors

Clinical Approach

• Is the tumor functional?
• Is the tumor malignant
Surgical Management of Insulinoma

- Complete exposure of the pancreas
- Inspection and bimanual palpation
- *Intra-operative ultrasound of the pancreas*
- Definitive localization of the functioning tumor
- Enucleation versus pancreatic resection
- Special considerations: MEN 1, malignant insulinomas
Operative Approach to Localize Insulinoma

Evaluate entire pancreas by inspection, digital palpation, and intra-operative US

Photo courtesy, Dr. Gerard Doherty
Surgical Treatment Options

- Enucleation
- Distal Pancreatectomy
- Pancreaticoduodenectomy
- Laparoscopic distal pancreatectomy
Enucleation

from Clark OH, Duh Q-Y Endocrine Surgery W.B. Saunders and Co. 1997
Enucleation of insulinoma from pancreatic tail

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Insulinoma

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The Role of Laparoscopy for PNETs

- Especially good for small, distal lesions
- Can also enucleate
- Well-suited for distal pancreatectomy/splenectomy

Distal Pancreatectomy

Cameron, JL. Atlas of Surgery BC Decker, Inc. 1990
Distal Pancreatectomy/Splenectomy
Surgical Specimen

Pancreatic Margin >1 cm
Spleen
Tumor

Courtesy James Howe, MD
Pancreatic NET – tail of the pancreas
Laparoscopic Distal Pancreatectomy/Splenectomy
Neuroendocrine tumor of the distal Pancreas
Pancreatico-duodenectomy
Whipple Operation

Cameron JL Atlas of Surgery BC Decker, Inc. 1990
Complications

- Death (~3%)
- Delayed Gastric emptying (8-45%)
- Pancreatic leak (10-33%)
- Blood transfusion (50%)
- Hemorrhage (3-13%)
- Bile duct leak (<5%)
- Gastric/duodenal leak (rare)
- Readmission (15%)
NET in Patients with MEN 1 – Special Considerations

Islet Cell Hyperplasia in MEN 1
Radiographic Imaging Tests for Neuroendocrine Tumors in Patients with MEN1

- Computed tomography scan (CT) with pancreas protocol
- Endoscopic ultrasound (EUS)
- Somatostatin receptor scintigraphy scan (Octreotide scan)
- (Provocative) Arteriography
- Intraoperative US
### Results of Imaging Tests for Localization of NET in Patients with MEN 1

<table>
<thead>
<tr>
<th>Imaging Test</th>
<th>n</th>
<th>True Positives (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive Trans-abdominal US</td>
<td>2</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>CT scan</td>
<td>17</td>
<td>10 (59%)*</td>
</tr>
<tr>
<td>Octreoscan</td>
<td>13</td>
<td>9 (69%)</td>
</tr>
<tr>
<td>MRI</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Invasive Pancreatic Arteriogram</td>
<td>3</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Provocative Angiography</td>
<td>2</td>
<td>2 (100%)#</td>
</tr>
<tr>
<td>Intra-operative US</td>
<td>18</td>
<td>17 (94%)</td>
</tr>
</tbody>
</table>

*true positives reflect those CT scans that revealed the largest or most clinically important pancreatic NET
#Selective intra-arterial calcium gluconate achieved accurate regional localization of insulinomas in two patients

Surgical Management of Neuroendocrine Tumors in Patients with MEN1

- Role of diagnostic staging laparoscopy
- Complete operative exposure of pancreas
- Intraoperative US
- Enucleation of small benign tumors with preservation of pancreatic function
- Major pancreatic resection for large tumors or malignant neuroendocrine tumors
Management of Pancreatic Neuroendocrine Tumors in MEN 1: Enucleation vs. Pancreatic resection

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Surgical Decision Making – MEN 1

- Remove imageable tumors (>1.0-2.0 cm)
- Individualize care based on age, health status, tumor size, clinical syndrome, evidence of metastasis
- Oncologically sensible operation aimed at minimizing morbidity and preserving pancreatic function

Malignant Insulinomas

- Malignancy is determined by the presence of local invasion or metastases.

- While 10% of all insulinomas are malignant, 30% of patients with metastatic disease are still resectable for cure.

- Incomplete resection fails to control symptoms but does improve survival.

- Chemotherapy may improve patient symptoms but has no effect on survival.
Summary

- Insulinomas result are rare, and may result in bizarre, striking or atypical signs and symptoms.
- The diagnosis may be delayed until the association of hypoglycemia with fasting is recognized, and other more likely causes excluded.
- Establishing the diagnosis may require a careful, supervised fast.
- Biochemical confirmation of endogenous hyperinsulinism should be made prior to obtaining extensive imaging or localizing procedures.
Summary II

- High resolution, triple phase CT and EUS best preoperative non-invasive imaging tests
- Experience and availability of surgeon-performed intraoperative US of the pancreas is critical for accurate intraoperative identification of insulinomas
- Surgical excision is the only cure for insulinoma
Acknowledgements

- Endocrine Surgery Fellow, Baylor Scott & White Health
  - Henry Reinhart, MD