Clinical Approach to Hypercalcemia
For the Primary Care Provider

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Objectives

- Recognition of pitfalls of diagnosis of hypercalcemia
- Understand the benefits of surgical intervention for primary hyperparathyroidism

Disclosures:
  - None
“Only the man who is familiar with the art and science of the past is competent to aid in its progress in the future.”

Theodore Billroth, Vienna Austria, 19th century
1850; Richard Owen
London Zoo

Ivar Sandstrom, 1877-80
Dissected >50 bodies
Evolution

- First successful Parathyroidectomy:
  - 1925 by Felix Mandl in Austria
  - For patient with Osteitis Fibrosa Cystica
American Contributions

- Charles Martell, Sea Captain in New England
  - Significant bone disease; lost 7 inches of height
- Parathyroidectomy performed in May 1926
  - 7 operations later, he was cured…
    - Culprit: Ectopic gland in the chest
Evolution of the Biochemistry

- Recognition of hypercalcemia
  - Clinical
  - Incidental discovery

- PTH Assays
  - Bioassay evolved to a radio-immunologic assay to Immunometric assay:
    - Allows for specific identification of the active portion of the molecule
    - Rapid: 15-30 min
  - Pitfalls: Antibody formation may alter results
PTH Assays

- Discovering Abnormal Ranges
  - Plotting Calcium with PTH
  - Surgical findings compared to pre-op levels

5-20% of patient with mild HPTH may have normal PTH levels
Diagnosis of Hypercalcemia
Calcium regulation

- Increased calcium in blood
- Parathyroid hormone
- Calcium reabsorption from bones
- Calcium reabsorption and vitamin D hydroxylation in kidneys
- 1,25 hydroxy-vitamin D
- Calcium absorption from intestines
Hypercalcemia

- PHPTH, Malignancy, FHH
- Granulomatous disease: sarcoidosis, tuberculosis, berylliosis
- Endocrine disorders: Addison’s disease, hyperthyroidism, hypothyroidism, neuroendocrine tumors
- Medications: Thiazides, lithium, calcium
- Increased dietary intake; Milk-alkali syndrome
- Immobilization; Paget’s disease
Hyperparathyroidism

- Primary
  - Autonomous production of Parathyroid Hormone (PTH)
  - Elevation of calcium and PTH
Hyperparathyroidism

- Primary
- Secondary
  - Elevation of PTH in response to a physiologic process
    - Renal Failure
    - Vitamin D Deficiency
Hyperparathyroidism

- Primary
- Secondary
- Tertiary
  - Autonomous production from a previously hyperplastic gland
    - Typically occurs after renal transplant
Primary Hyperparathyroidism

- Derangement of calcium-controlled release of PTH from parathyroid glands
  - Variable sensitivity to calcium
  - Calcitriol suppresses PTH mRNA
  - Adenomas have dysfunctional calcitriol receptors
    - Calcium suppression remains, although altered
- May be one or more glands involved
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Signs</th>
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<tbody>
<tr>
<td>Fatigue/Exhaustion</td>
<td>Nephrolithiasis</td>
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<tr>
<td>Weakness</td>
<td>Hematuria</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>Bone fracture</td>
</tr>
<tr>
<td>Polyuria/Nocturia</td>
<td>Gout</td>
</tr>
<tr>
<td>Bone pain/Joint pain</td>
<td>Joint swelling</td>
</tr>
<tr>
<td>Back pain</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Constipation</td>
<td>Duodenal Ulcer</td>
</tr>
<tr>
<td>Depression</td>
<td>Gastric Ulcer</td>
</tr>
<tr>
<td>Memory loss</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>Hypertension</td>
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<tr>
<td>Nausea/Heartburn</td>
<td></td>
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<tr>
<td>Pruritis</td>
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Hyperparathyroidism is characterized by increased parathyroid hormone (PTH) production, which stimulates bone resorption, renal calcium reabsorption, and intestinal phosphorus excretion. This leads to hypercalcemia and hypophosphatemia. Adenomas and hyperplasia are common causes of hyperparathyroidism.
Diagnosis

- Diagnosis:
  - Calcium, PTH
  - Vitamin D
  - Renal panel
    - Phosphorous and Increased Chloride:Phos (>33)
  - 24 hour urine Calcium
  - Alkaline Phosphatase
  - Protein electrophoresis, urine and serum
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</thead>
<tbody>
<tr>
<td>Serum Ca (&gt; normal)</td>
<td>1-1.6 mg/dL</td>
<td>1.0 mg/dL</td>
<td>1.0 mg/dL</td>
<td>≥1.0 mg/dl</td>
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<tr>
<td>24-h Urine Calcium</td>
<td>&gt;400 mg/d</td>
<td>&gt;400 mg/d</td>
<td>Not indicated</td>
<td>&gt;400 mg/d*</td>
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<tr>
<td>Creatinine Cl</td>
<td>Reduced 30%</td>
<td>Reduced 30%</td>
<td>Reduced to &lt;60 ml/min</td>
<td>GFR&lt;50 ml/min*</td>
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<tr>
<td>BMD</td>
<td>Z-score &lt;-2.0 forearm</td>
<td>T-Score &lt;-2.5 any site</td>
<td>T-Score &lt;-2.5</td>
<td>T-score &lt;2.5 or fx</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50 **</td>
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</table>
Additional Considerations

- ‘Silent’ renal involvement
  - Stones, calcinosis, impaired renal function
- Osteopenia, fractures
  - Bone density improves and risk of fracture decreases even in ‘normal’ bone
- Neurocognitive symptoms
  - 3 Randomized controlled trials demonstrate benefit
- Cardiovascular disease
- Muscle fatigue/sleep disturbances, GERD, fibromyalgia
Hot off the Podium...

AAES 2018
End-Organ Effects

- End-Organ Effects of Primary HPTH: A Population-based Study
  - UCLA/Kaiser of SoCal studied nearly 20 years of data
  - 12,800 patients → 4,103 (32%) had pre-existing end-organ effects:
    - Osteoporosis 22%; Nephrolithiasis 10%; Hypercalciuria 4%
  - Remaining 8,697 patients, 27% progressed
    - Renal impairment was most common sign of damage (13%),
      Osteoporosis 10%, nephrolithiasis 3% and hypercalciuria 1%
- End-organ damage can occur 5 years prior to the diagnosis being made
Bone Density:

- Bone Mineral Density Changes after Curative Parathyroidectomy: An Analysis of Patients with Primary Hyperparathyroidism According to Biochemical Profiles
  - Patients with classic presentation – Hypercalcemia and high PTH had improvement of BMD at all sites BUT RADIUS
Future Directions:

- Growing Human Parathyroids in a Microphysiological System: A Novel Approach to Understanding and Developing New Treatments for Hyperparathyroidism
  - Cultured cells from 20 hyperparathyroid patients
  - Grew into pseudoglands after 2 weeks
  - PTH and calcium response did decline over time
- Future application – evaluate PTH effects on other tissue types
Parathyroidectomy

- Minimally Invasive Parathyroidectomy
  - 85% single gland
- Bilateral Exploration
  - 15% multi-gland disease
- Localization studies
  - Sestamibi parathyroid scan +/- SPECT imaging
  - US – preferably surgeon performed
Imaging
Additional Tests

- 4-D CT
- MRI
- CT
- Venous Sampling
Medical Management

- Gently correct Vitamin D
- No restriction on Calcium intake

- For patients who are NOT surgical candidates:
  - Aim to mitigate effects of the disease
  - Monitor for severe elevations of calcium
Hypercalcemic Crisis

- Severe hypercalcemia with symptoms
- Hydration, hydration, hydration
- Lasix
- Calcitonin
- IV Bisphosphonates
  - Pamidronate
Intra-Operatively

- Goals:
  - Normal calcium
  - Clinically improved patient
- Minimally Invasive approach vs Sub-total Resection
When “bad” things happen…

- Identify normal anatomy
  - Utilize histology
- Recognize tools available – PTH assay
- Consider embryology and typical ectopic locations
  - Thymus
  - Intrathyroidal
  - Carotid sheath
- Decide when to stop
Expectations of Surgery

- Normal Calcium and PTH
- Fast recovery
  - Outpatient
  - 1-2 weeks of ‘down’ time
  - Calcium supplementation for bone regeneration
- Follow calcium and PTH at 6 months
- Minimal scarring for most
Persistent or recurrent disease

- Consider the risk-benefit analysis
- Localize a target
  - Can involve multiple imaging tests
- Recovery can be more difficult
- Success rates are more difficult to achieve
Technological Advances
Minimally invasive video-assisted parathyroidectomy: lessons learned from 137 cases

Paolo Miccoli, MD, Piero Berti, MD, Massimo Conte, MD, Marco Raffaelli, MD, Gabriele Materazzi, MD

Journal of the American College of Surgeons
Volume 191, Issue 6, Pages 613-618, December 2000
Trans-oral Approach

- Pioneered by Lee and colleagues at Korea University College of Medicine
  - First trial in Humans published in 2014
  - Initially piloted for hemi-thyroidectomy for small benign nodules
  - Subsequently expanded to larger lesions and malignant lesions
  - Expanded to parathyroid disease
  - Some techniques utilizing Robotic platform
Objectives

- Recognition of pitfalls of diagnosis of hypercalcemia
- Understand the benefits of surgical intervention for primary hyperparathyroidism
Take Home Message:

- Calcium abnormalities can be confusing and significant
  - Always dig deeper
  - Feel free to ask for consultation
- Surgery can provide benefit with minimal to moderate risk
- Best way to locate a parathyroid gland is to locate a high volume surgeon!
Questions?