Objectives

1. Diagnostic cases illustrating parathyroid disease from the simple to the challenging
2. Parathyroid tumors with normal calcium or PTH
3. Imaging in parathyroid disease
4. Surgical options for primary hyperparathyroidism

Case 1

A 43 year old woman with 3 children has been experiencing profound fatigue, muscle aches, and forgetfulness. Her PCP palpates a fuller neck and orders a thyroid ultrasound.

ENT PARATHYROID LABS

<table>
<thead>
<tr>
<th>Latest Ref Rng</th>
<th>10/31/2013</th>
<th>11/18/2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>3.5-10.2 mg/dL</td>
<td>11.1 (H)</td>
</tr>
<tr>
<td>Phos</td>
<td>2.4-4.7 mg/dL</td>
<td>1.0 (L)</td>
</tr>
<tr>
<td>PTH</td>
<td>15.0-65.0 pg/ml</td>
<td>426.5 (H)</td>
</tr>
<tr>
<td>Ionized Calcium</td>
<td>1.14-1.28 mmol/L</td>
<td>1.42 (H)</td>
</tr>
<tr>
<td>VIt D 25-Hydroxy</td>
<td>30-80 ng/mL</td>
<td>21.1 (L)</td>
</tr>
<tr>
<td>VIt D 1, 25-dihydroxy</td>
<td>15 - 75 pg/mL</td>
<td>135 (H)</td>
</tr>
<tr>
<td>24 hr Urine Calcium</td>
<td>100-300 mg/24h</td>
<td>402 (H)</td>
</tr>
<tr>
<td>24 hr Creatinine</td>
<td>0.50-1.60 g/24h</td>
<td>1.13</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.80-1.10 mg/dL</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Case 1

A 43 year old woman with 3 children has been experiencing profound fatigue, muscle aches, and forgetfulness. Her PCP palpates a fuller neck and orders a thyroid ultrasound.

IOPTH

<table>
<thead>
<tr>
<th>556 pg/ml</th>
<th>25 pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/22/2013</td>
<td>8.8 calcium</td>
</tr>
<tr>
<td>29.0 PTH</td>
<td></td>
</tr>
</tbody>
</table>
Case 1

A 43 year old woman s/p parathyroidectomy undergoes long-term monitoring for durable cure of her hyperparathyroidism.

Labs at 6 months post-op and annually

Parathyroid Disease Evaluation

<table>
<thead>
<tr>
<th>Serum</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>24 hr calcium</td>
</tr>
<tr>
<td>Ionized calcium</td>
<td>24 hr creatinine</td>
</tr>
<tr>
<td>Intact PTH</td>
<td></td>
</tr>
<tr>
<td>25-hydroxy vitamin D</td>
<td></td>
</tr>
<tr>
<td>1,25-dihydroxy vitamin D</td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
</tr>
</tbody>
</table>

Primary Hyperparathyroidism is Both Under-Diagnosed and Under-Treated

1 of 500 women
1 of 1000 men
over age 50 years

Indications for Parathyroidectomy in Primary Hyperparathyroidism (asymptomatic)

- Serum calcium > 1 mg/dL above normal
- An episode of hypercalcemic crisis
- Reduced creatinine clearance (<30% normal)
- Low bone density (T score < -2.5 at lumbar spine, hip or wrist)
- Age < 50
- Medical surveillance not desirable or possible
  - (Clinical manifestations/ complications)
  - (Hypercalciuria > 400 mg/day)

Indications for Parathyroidectomy in Primary Hyperparathyroidism (asymptomatic)

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (higher limit of normal)</td>
<td>1.6-2.5 mg/dL</td>
<td>2.5-3.0 mg/dL</td>
<td>2.5-3.0 mg/dL</td>
</tr>
<tr>
<td>24-hour urine calcium, creatinine, and BMD</td>
<td>400 mg/dL</td>
<td>400 mg/dL</td>
<td>400 mg/dL</td>
</tr>
<tr>
<td>25-hydroxy vitamin D</td>
<td>20 ng/mL</td>
<td>30 ng/mL</td>
<td>30 ng/mL</td>
</tr>
<tr>
<td>1,25-dihydroxy vitamin D</td>
<td>20 pg/mL</td>
<td>20 pg/mL</td>
<td>20 pg/mL</td>
</tr>
</tbody>
</table>

AAES 2013
Chicago, IL

Hyperparathyroidism
In EMR
60% no PTH
1/3 have PHP

NIH Consensus 1990
AACE/AAES Position Statement 2005
NIH/NIDDK 2002
3rd International Workshop (Bilezikian et al JCEM) 2009
Only 50% of patients satisfying criteria for parathyroidectomy actually get surgery.

Roles of Preoperative Imaging for PHP

- Assist surgeon in identifying anatomic location of abnormally functioning or enlarged parathyroids
  ✓ guides focally directed surgeries
  ✓ aids conduct or sequence of exploration
  ✓ reduces OR time
  ✓ “challenge of the hunt” vs “smooth sailing”

- Alert to potential ectopic disease, particularly in the mediastinum
- Assess the feasibility of surgery in re-operative cases
- Exclude important thyroid pathology

US and Sestamibi Imaging for PHP

- **Ultrasound**
  - images neck region only, not mediastinum
  - cost-effective, painless, non-invasive
  - no radiation exposure
  - accuracy is highly operator-dependant

- **99mTc-Sestamibi**
  - most popular procedure
  - quality varies widely among institutions
  - many types of scans
  - major advantage is identifying ectopic sites

Underutilization of Parathyroidectomy in Elderly Patients with Primary Hyperparathyroidism

Bian Wu, Philip L. Haigh, Roy Hwang, Philip H. G. Ituarte, In-Lu Amy Liu, Theodore J. Nahl, and Michael W. Yeh

Conclusions: PHP is undertreated in the elderly. We observed a progressive age-related decline in PTH rate that renders patients aged 70+ unlikely to have definitive treatment, irrespective of comorbidity and eligibility for surgery. (*U Clin Endocrinol Metab* 55: 4324–4330, 2010)

Ultrasound and Sestamibi imaging should only be performed once biochemical diagnosis of PHP is known

+ imaging studies do not confirm diagnosis
- imaging studies do not exclude diagnosis

Expectations for Accuracy in US and Sestamibi Imaging for PHP

- **Ultrasound**
  - Sn 82% and SP 90% (PPV 70% for SA, 50% for MGD) identifies coexisting thyroid disease (20-40%)/cancer (4%)

- **Sestamibi**
  - most centers 50-75% accuracy
  - some series >90% accuracy known to be as low as 27-55% for multigland disease

- **Both**
  - 70-90% will be positive and definitions of success vary

**Perioperative Imaging Studies Used to Evaluate Patients with Hyperparathyroidism**

- Sestamibi + US: 62%
- Sestamibi: 26%
- Other 10%
- 4d-CT, MRI, PET, FNA, venous sampling

US only 2%

Greene JACS 2009

**Normal Parathyroids are NOT Imaged**

**Ultrasound as Initial and Primary Imaging Modality for PHP**

- US shows single adenoma, MIBI scan suggests more sites in 10% (correctly in only 2.5%)
- US shows MGD, but MIBI single adenoma, MIBI wrong in 50%
- US negative, MIBI helpful in 50%

Aliyev et al ACS 2012

**3 Circles Sign:**
Sonographic Appearance of Parathyroid Adenoma, Carotid Artery and Jugular Vein in Transverse Imaging


**Correlation of Parathyroid Sonographic Distribution to Embryologic Origin**
Parathyroid Ultrasound Identifies Thyroid Pathology
(Milas Thyroid 2005, Morita Surgery 2008, Aliyev ACS 2012)

33% thyroid nodules
(½ FNA, ⅓ surgery)
7% thyroid cancer

Case 2
A 60 year old man has hypercalcemia detected on annual exam and PHP is diagnosed. Referred from Alaska desiring “mini” parathyroidectomy.
Parathyroid Sestamibi Imaging

2-D Planar Sestamibi Scan with Initial and Delayed Imaging

Sestamibi Iodine Subtraction Scan with SPECT imaging

Sestamibi Iodine Subtraction Scan with SPECT imaging

$^{99}$Tc Sestamibi | $^{123}$ Subtraction
Radionuclide imaging for hyperparathyroidism (HPT): Which is the best technetium-99m sestamibi modality? (Sharma et al. Surgery 2006)

Sestamibi Iodine Subtraction Scan with SPECT Imaging and CT Co-localization

99Tc Sestamibi - Iodine  CT Co-localization

Sestamibi Imaging in Secondary Hyperparathyroidism

Typical negative findings  Rare positive study

99Tc-Tetrofosmin  99Tc-Sestamibi
4-Dimensional CT Imaging

3-D CT method with 4th dimension representing changes in perfusion of contrast over time: hyperfunctioning parathyroids have rapid uptake and washout.

3-D reconstruction/rendering based on 4-D CT imaging

1.25 mm Axial
2.5 mm sagittal coronal oblique

Strategy for Re-operative Parathyroidectomy

CONFIRM Dx → OBTAIN ALL PMH, PSH, records → FORMULATE PLAN by CLINICAL SCENARIO

RE-FORMULATE PLAN by LOCALISING STUDIES

IMAGING:

Surgery

yes → 2 concordant studies?

no → VENOUS SAMPLING

Negative Discordant Indeterminate Unusual

Region seen?

yes →

no →

Challenging Parathyroid Localization

Phenotypes of Primary Hyperparathyroidism

Calcium (mg/dl)

PTH (pg/ml)

Ca ≤ 10.5

Ca > 10.5

PTH > 60

PTH ≤ 60

2° HPT

NormoCa HPT

1° HPT

Normal

Normohormonal HPT

The phenotype of primary hyperparathyroidism with normal parathyroid hormone levels: How low can parathyroid hormone go?

The phenotype of primary hyperparathyroidism with normal parathyroid hormone levels: How low can parathyroid hormone go?


Background: While normoCa hyperparathyroidism is well recognized in primary hyperparathyroidism (PHPT), its impact on calcium balance is still largely undefined. In this study, we aimed to determine the clinical and biochemical characteristics of normoCa hyperparathyroidism (NormoCa HPT) and compare it with 2° primary hyperparathyroidism (2° HPT) and normoCa HPT.

Methods: A prospective study of 100 patients with PHPT and normal serum calcium levels was conducted. Patients with intact parathyroid hormone (iPTH) levels >100 pg/ml were excluded. The primary outcome was the identification of NormoCa HPT, defined as normal serum calcium levels, iPTH levels >100 pg/ml, and intact parathyroid hormone (iPTH) levels >100 pg/ml. The secondary outcome was the determination of the prevalence of NormoCa HPT.

Results: All 100 patients had normal serum calcium levels. Of these, 23 patients (23%) had iPTH levels >100 pg/ml, 21 patients (21%) had normochromic normocytic anemia, and 10 patients (10%) had normal renal function. No patient had a history of kidney stones. The prevalence of NormoCa HPT was 30% (95% CI, 18%-45%). The prevalence of NormoCa HPT was higher in patients with iPTH levels >100 pg/ml (36%) than in those with iPTH levels ≤100 pg/ml (18%). The prevalence of NormoCa HPT was also higher in patients with normal renal function (33%) than in those with abnormal renal function (11%). The prevalence of NormoCa HPT was similar in patients with normochromic normocytic anemia (31%) and those without (30%).

Conclusion: The prevalence of NormoCa HPT is comparable to that of 2° HPT and normoCa HPT. Although normoCa HPT is rare, its recognition is important for the diagnosis and management of PHPT.

Calculating an individual maxPTH to aid diagnosis of normocalcemic primary hyperparathyroidism

Judy Jue, MD,* Jamie Mitchell, MD,* Jamie Skin, MD,* Eric Bebe, MD,* Allen Le, MD,* and Maya Win, MD,* Cleveland, OH, and Portland, OR

Background. We aimed to validate a nomogram for diagnosing primary hyperparathyroidism (PHPT), particularly when normocalcemic PTH and vitamin D (VitD25) deficiency coexist.

Methods. The nomogram calculates modified upper limits of normal PTH values for each factor using maxPTH = 120 - (6 x Ca) - (½ x VitD25) + (¼ x Age). PHPT was suspected when serum PTH exceeds maxPTH. Normocalcemic PHPT (NCPHP) was defined in athletes normal serum calcium (8.5-10.5 mg/dL) with PTH > 60 pg/mL, proportionally and VitD25 deficiency (<31 ng/mL).

Results. A total of 173 patients had operatively and biochemically proven PHPT. Overall and including those with classical presentation (high serum levels of calcium and PTH), the nomogram predicted PHPT in 97% patients. A total of 56 had NCPHP: 45 with low VitD25 levels (27.5 ± 7.9 ng/mL), male idiopathic PHPT, and 19 with normal VitD25 levels. Although serum calcium concentrations were equivocal in one 2 groups (10.3 ± 0.4 mg/dL), PTH was greater in patients with concurrent VitD25 deficiency (129 ± 92 pg/mL, P = 0.002). However, when used to calculate maxPTH, the nomogram predicted PHPT correctly in all 66 PHPT patients (100%).

Conclusions. The maxPTH nomogram functions as a tool to classify patients with PHPT and may aid in the diagnosis of NCPHP regardless of vitamin D status and repletion, ensuring primary providers and surgeons utilize on appropriate and timely PHPT management. (Surgery 2012; 151:136-42.)

maxPTH* =

\[120 - (6 \times \text{Ca}) - \left(\frac{1}{2} \times \text{VitD25}\right) + \left(\frac{1}{4} \times \text{Age}\right)\]

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**Case 3**

A 73 year old woman with osteoporosis is screened for underlying parathyroid disease.

<table>
<thead>
<tr>
<th><strong>ENT PARATHYROID LABS</strong></th>
<th>Latest Ref Rng</th>
<th>5/13/2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>8.6-10.2 mg/dL</td>
<td>9.2</td>
</tr>
<tr>
<td>Phos</td>
<td>2.4-4.7 mg/dL</td>
<td>3.3</td>
</tr>
<tr>
<td>PTH</td>
<td>15.0-85.0 pg/mL</td>
<td>134.0 (H)</td>
</tr>
<tr>
<td>Ionized Calcium</td>
<td>1.141-1.28 mmol/L</td>
<td>1.12 (L)</td>
</tr>
<tr>
<td>Vit D 25-Hydroxy</td>
<td>30-60 ng/mL</td>
<td>32.8</td>
</tr>
<tr>
<td>Vit D 1, 25-dihydroxy</td>
<td>15-75 pg/mL</td>
<td>36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calcium (mg/dL)</th>
<th>Vitamin D25 (ng/mL)</th>
<th>PTH (pg/mL)</th>
<th>maxPTH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monitored Group (n=14)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.4 ± 0.4</td>
<td>30 ± 15</td>
<td>84 ± 30</td>
<td>61</td>
</tr>
<tr>
<td><strong>True 2o HPT (n=7)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.6 ± 0.5</td>
<td>42 ± 7</td>
<td>44 ± 19</td>
<td>55</td>
</tr>
<tr>
<td><strong>NCPHP (n=7)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.6 ± 0.5</td>
<td>48 ± 18</td>
<td>108 ± 38</td>
<td>51</td>
</tr>
</tbody>
</table>

p-value (t-test) 1.0 0.4 **0.002** n/a
**Using maxPTH to Diagnose NCPHP**

- **Ionized Ca**
  - high → **Suspect 1st HPT** → **Refer to Parathyroid Surgeon**
  - normal or low

- **Vit D25**
  - normal or high → **Calculate maxPTH** → **Suspect NCPHP if labPTH > maxPTH**
  - low

  **“Replete vit D25” “Recalculate maxPTH” “Reconsider”**

**Primary Hyperparathyroidism (PHP): Patterns of Disease**

- **SINGLE ADENOMA**
  - 70-95%

- **DOUBLE ADENOMA**
  - 2-15%

- **HYPERPLASIA**
  - 10-30%

**Primary Hyperparathyroidism: Philosophical Approaches to Surgery**

- **Focal**
- **Unilateral**
- **Bilateral (BE)**
- **“Limited” (LE)**

**Historical Evolution of Parathyroid Surgery**

- 1875
- 1932
- 1974
- 1990
- 1998
- 2010

**Historical Evolution of Parathyroid Surgery**


**De-evolution of Parathyroid Disease Severity**

- Nice big parathyroid adenoma severe symptomatology Ca=12 mg/dl
- Multigland hyperplasia “apparently” asymptomatic Ca=10.8 mg/dl, normal

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**De-evolution of Parathyroid Disease Severity**


**Mazzaglia Arch Surg 2008**
Modern Options for Parathyroid Surgery

- Radioguided
- Video-assisted MIP
- Endoscopic gas vs gasless
- Selective/ “image-directed”/ targeted
- Focused open lateral
- Open anterior minimally-invasive
- Robotic
- Focal without IOPTH
- Trans-areolar/ transoral
- Bilateral
- “MIPS”

Parathyroid Ultrasound Imaging
Histology Cannot Distinguish Adenomas from Multigland Disease or Define the Clinical Etiology (
\textsuperscript{1}\textdegree vs \textsuperscript{2}\textdegree vs MEN)
Your patients

35 yo woman with PHP, known MEN I kindred

24 yo woman with 10 yr dialysis history now has high calcium, PTH 5000

Four gland parathyroid hyperplasia at surgery
Summary: Primary Hyperparathyroidism

- Common but under-recognized and under-referred
- Diagnosis ranges from simple to challenging (relies on brain and lab power not imaging)
- Parathyroid surgery offers low-risk and durable cure of disease yet remains underutilized

The OHSU Thyroid and Parathyroid Center is designed to provide comprehensive, streamlined care for patients with thyroid and parathyroid diseases.

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Thank You