Hyperparathyroid: 
Primary vs “non”primary

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Disclosure

• Speaker’s bureau
  /Advisory board
  /honorarium:
  – Abbvie
  – Takeda Pharm.
  – Amarin corp.

Extracellular fluid calcium
- 50% bound
  - albumin
  - phosphorus and citrate
- 50% ionized (free)
Calcium homeostasis

- Function
  - Regulates ion transport across cell membrane
  - Normal muscle and nerve activity
  - Cofactor to enzymes

- 3 regulating hormones
  - PTH
  - Vitamin D
  - Calcitonin

- Responds to ionized Ca

Calcium homeostasis

- Parathyroid hormone (PTH)
Calcium homeostasis

- Vit D

Calcium homeostasis

- Calcitonin
  - Secreted by thyroid C cells (parafollicular cells)
  - Counter-regulatory effect of PTH
  - Little role in calcium homeostasis
    - post-thyroidectomy
    - Metastatic medullary thyroid cancer
  - Clinical use: medullary thyroid cancer marker

Case #1

- 47yo female was referred by her PCP due to hypercalcemia that was found during routine physical exam.
- ROS: (+) for mild fatigue. (-) HA, depression, constipation, joint pain.
- Patient denies history of kidney stones, bone fractures. No BMD was performed in the past.
- No medication. Describes herself as healthy person.
Case #1

• Lab from outside
  – Calcium 11.2 H (8.2-10.2)
  – GFR >60
  – Albumin 4.0 (3.5-4.8)
  – Alk. Phos. 182 H (25-160)
  – LFTs nml (CMP otherwise nml)
  – CBC/TSH/lipids nml

DDx for hypercalcemia

Parathyroid related
  – Primary hyperparathyroidism
  – Solitary adenoma
  – Multiple endocrine neoplasia
  – Lithium therapy

Malignancy related
  – Solid tumor with metastasis (breast)
  – Solid tumor with humoral mediation of hypercalcemia (lung, kidney)
  – Hematological malignancies (multiple myeloma, lymphoma, leukemia)

Associated with renal failure
  – Severe secondary and tertiary hyperparathyroidism
  – Aluminium intoxication
  – MDRD-akali nephronie

Vitamin D related
  – 1,25(OH)2 vitamin D, sarcoidosis and other granulomatous diseases
  – Idiopathic hypercalcemia of infancy

Adrenal Insufficiency

Associated with high bone turnover
  – Hyperparathyroidism
  – Immobilization
  – Thyrotoxicosis
  – Vitamin A intoxication

Case #1 (cont.)

• Labs
  – Calcium 11.3 H (8.2-10.2)
  – PTH 117 H (15-65)
  – Vitamin D 43 (30-100)
  – Phosphorus 2.5 (2.3-3.3)
  – 1,25(OH)2 vitD 71H (20-60)
  – 24hr urine Ca 440 H (100-300mg/day)
  – CBC/CMP/TSH/FT4/SPEP wnl
Case #1 (cont.)

- Labs
  - Calcium 11.3 H (8.2-10.2)
  - PTH 117 H (15-65)
  - 1,25(OH)2 vitD 71H (20-60)
  - 24hr urine Ca 440 H (100-300mg/day)
  - Diagnosis?

Hyperparathyroidism

- Primary
  - Normal feedback of calcium is disturbed, causing increased production of PTH
- Secondary
  - Defect in mineral homeostasis leading to a compensatory increase in parathyroid gland function
- Tertiary
  - After prolonged compensatory stimulation, hyperplastic gland develops autonomous function

Primary HyperPTH

- Incidence increases dramatically after age of 50.
- >40yo, M:F ratio is 1:3
- 80-85% by isolated adenoma, 15-20% by hyperplasia, <1% by parathyroid cancer
### Effects of hyperparathyroidism

- **Kidney**
  - Hypercalciuria/Kidney stones
  - Renal parenchymal calcification (nephrocalcinosis)
- **Skeletal**: Increased bone resorption
- **GI**
  - Constipation, anorexia, N/V
  - Pancreatitis, peptic ulcer disease
- **Neuromuscular**
  - CNS depression: lethargy, coma (if severe)
  - Muscle weakness, hyporeflexia

### Case #1 (cont.)

- **Further testing:**
  - Parathyroid US
  - Technetium (99mTc) Sestamibi scan
  - MRI or CT
- **Other testing that can be considered:**
  - BMD (3 view)

### Treatment

- **Surgery vs Medical surveillance**
- **Surgical indication (NIH guideline 2002)**
  - Serum Ca >1mg/dL above ULN
  - 24hr urine Ca >400mg/dL
  - Creatinine clearance reduced by 30%
  - BMD T-score < -2.5 at any site
  - Age < 50

*J P Bilezikian et al. J Clin Endocrinol Metab 87:5353, 2002*
Medical surveillance

- serum calcium q6months
- Serum creatinine q1year
- BMD q1year on lumbar spine/hip/forearm
- No longer recommended: 24hr urinary Ca/creatinine clearance/abdominal xray

JP Bilezikian et al: J Clin Endocrinol Metab 87:5353, 2002

Medical surveillance

- Ensure hydration
- Avoid diuretics/prolonged immobilization
- Do not exceed 800mg/day of Calcium
- SERM/bisphosphonate/Calcimimetics

Variant of PHPT

- Familial benign hypocalciuric hypercalcemia (FBHH)
  - Inherited autosomal dominant trait
  - Loss of function mutations in CaSR (PTH/renal)
  - Lifelong asymptomatic hypercalcemia
  - Usually mild (10.5-12mg/dL)
  - PTH is normal/slightly elevated
  - Hypocalciuria (<50mg/24hr)
  - Sequencing of the CaSR gene commercially available
  - HOW TO TREAT???
Variant of PHPT

- Lithium induced
  - lithium raises CaSR threshold for PTH inhibition
  - Produces hypocalciuria → phenocopy of FBHH
  - Lithium also can unmask underlying PHPT
  - Alternate therapy/temporary cessation (consult with psychiatrist)
  - Underlying PHPT likely if Ca >11.5mg/dL

Case 2

- 27yo female was referred for hypercalcemia secondary to hyperparathyroidism. She is here to establish her care with endocrinologist.
- Reviewing her record, it correlates with parathyroid adenoma (serum work up, Sestamibi positive, US positive).
- She does have history of kidney stones x3, went to ER twice and it passed with hydration

Case 2 (cont.)

- ROS: she’s been amenorrheic for 15 months, neg pregnancy, currently sexually inactive. She does have breast discharge that she noticed for the past 6 months.
- She does have episodes of severe lightheadedness, anxious, sweaty which improves with OJ. She’s been struggling with nightmares and would wake up soaked wet.
Case 2 (cont.)

- Family history is positive for her father with brain tumor that was surgically treated. Her brother also had multiple kidney stones that required lithotripsies. She remembers her paternal aunt having issues with frequent hot flashes where her face would turn red.

MEN syndrome
(Multiple Endocrine Neoplasia)

- MEN 1 (P disease)
  - Parathyroid adenoma (most common)
  - Pituitary adenoma
  - EnteroPancreatic tumors
    - Insulinomas, Gastrinomas, Carcinoid tumors
  - Cutaneous tumors
    - Multiple angiofibromas, collagenomas, lipomas
MEN syndrome
(Multiple Endocrine Neoplasia)

• MEN 2A
  – MTC (100%)
  – Pheochromocytoma (~50%)
  – Parathyroid hyperplasia (15-20%)

• MEN 2B
  – MTC (100%)
  – Pheochromocytoma
  – Mucosal neuroma
  – Marfanoid habitus

Case 3

• 74yo male with long standing history of DM II/HTN/dyslipidemia and CKD IV
  – Ca 8.3 (8.2-10.2)
  – GFR 27 L (stage 4)
  – Vit D 41 (30-100)
  – PTH 243 H (15-65)
  – Phosphorus 3.7 H (2.3-3.3)
  – CMP otherwise nml

• Diagnosis?
Hyperparathyroidism

- **Primary**
  - Normal feedback of calcium is disturbed, causing increased production of PTH

- **Secondary**
  - Defect in mineral homeostasis leading to a compensatory increase in parathyroid gland function

- **Tertiary**
  - After prolonged compensatory stimulation, hyperplastic gland develops autonomous function

Secondary hyperPTH

- Compensatory hyperfunctioning of the parathyroid glands caused by hypocalcemia or peripheral resistance to PTH
- Reverses when correcting underlying cause
- Most common cause: CKD
- Less commonly: calcium malabsorption, vitamin D deficiency

hyperPTH from CKD

- Parathyroid gland activity increase in response to
  - Decreased calcitriol production
  - Decreased calcium
  - Increased phosphate
- Progressive disease if left untreated leading to metabolic bone disease, soft tissue calcification, increase CV morbidity/mortality
hyperPTH from CKD

• Medical management
  – Dietary phosphate restriction / phosphate binder
  – Vitamin D supplementation (calcitriol)
  – Calcimimetics/Dialysis
    (in CKD 5 with PTH 300-800)
  – Parathyroidectomy
    (in CKD 5 with PTH >800)

hyernerPTH from CKD

• Targets (from K/DOQI)

<table>
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<th>Stage</th>
<th>GFR</th>
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<th>Ca</th>
<th>PTH</th>
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<td>3.5-5.5</td>
<td>8.4-9.5</td>
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</tr>
</tbody>
</table>


Case 4

• 54yo female with recent diagnosis of osteopenia. Otherwise healthy.
  – Ca     8.4 (8.2-10.2)
  – GFR    >60
  – Vit D  19 L (30-100)
  – PTH    71 H (15-65)
  – Phosphorus 2.8 (2.3-3.3)
  – CMP otherwise nml
Case 4

• 54yo female with recent diagnosis of osteopenia. Otherwise healthy.
  – Ca  8.4 (8.2-10.2)
  – Vit D  19 L (30-100)
  – PTH  71 H (15-65)
• Diagnosis?

hyperPTH from low vitamin D

• Prevalent!!
  – Among 4495 adults in 2005-2006, 41.6% were <20ng/dL
  – Highest in AA (82.1%), followed by H (69.2%)
• Decreased Ca absorption in intestine leads to compensatory increase in PTH to get more calcium from bone and restrict renal excretion


Vitamin D replacement

• Rough estimate: every 100IU vitamin D increases serum vitamin D by 1 ng/dL
• Take 4000IU OTC vitamin D3 a day

• Rx Ergocalciferol (D2) 50,000IU/week?
• Non-Rx Colecalciferol (D3) 50,000IU/week?
  http://www.biotechpharmacal.com/catalog/d3-50-50000-iu/
hyperPTH from low vitamin D

• Repeat lab in 2-3 months
  – Ca 9.1 (8.2-10.2)
  – GFR >60
  – Vit D 53 (30-100)
  – PTH 31 (15-65)
  – Phosphorus 2.5 (2.3-3.3)
  – CMP otherwise nml

Tertiary hyperparathyroidism

• After prolonged compensatory stimulation, hyperplastic gland develops autonomous function.
• Massive hyperplasia and possibly adenomatous transformation.
• Calcium-mediated PTH suppression is lost in tertiary hyperparathyroidism leading to hypercalcemia in some patients.