

Hypercalcemia

Colorado ACP meeting

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Disclosures

None

Objectives

- Be able to effectively and efficiently evaluate hypercalcemia
- Be able to counsel patients on their diagnosis and prognosis
- Be able to counsel patients on their options for treatment



60 yo woman – evaluation of fatigue

- Anxiety, hypothyroidism, hypertension, obesity
- Levothyroxine, venlafaxine, HCTZ, losartan
- No recent illness
- Some increased stress
- Snores
- Fatigue is worse for 1+ year but most noticeable for 1-2 months

60 yo woman – evaluation of fatigue

- Weight is stable, exam is normal
- Labs 9 months previous TSH 4.16, prior 2.97
- Glucose 84, creatinine 0.66, CBC and LFT's normal
- Calcium 10.6

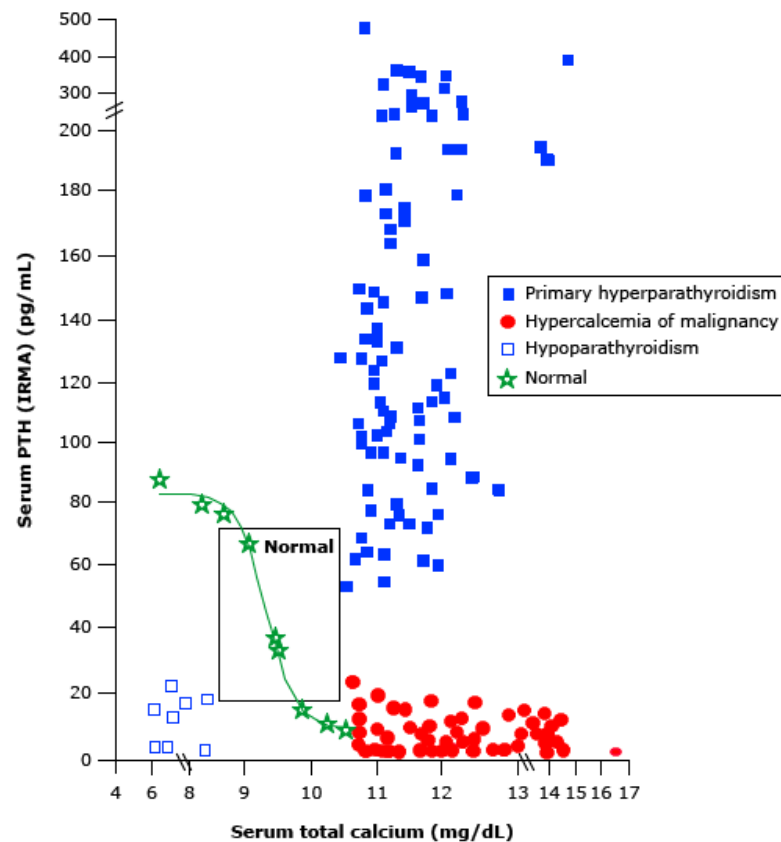
What do you order to evaluate her hypercalcemia

- Calcium, ionized calcium, PTH, PTHrp, Phosphate, creatinine, vitamin D(25-OH and 1,25 OH), 24 hr urine calcium and creatinine
- Calcium, phosphate, creatinine, PTH
- Calcium, creatinine, PTH, vitamin D (25OH)
- All of the above + sestamibi scan of neck

Etiology and Differentiation of Hypercalcemia

	Calcium	PTH	Vitamin D
Primary Hyperparathyroidism	Elevated	High normal or elevated	Normal or low
Malignancy	Elevated	Low (<20 ng/dl)	Depends on malignancy

Serum parathyroid hormone (PTH) concentrations in hypercalcemia and hypocalcemia



Serum PTH concentrations according to the serum total calcium concentration in various disease states. The normal range is shown in the white box. The sigmoidal curve (green stars) is derived from a calcium citrate infusion protocol administered to 38 normal subjects. Serum PTH and calcium values are low in hypoparathyroidism (open blue boxes) and high in primary hyperparathyroidism (blue squares). The serum calcium concentration is high and serum PTH is appropriately low in patients with non-PTH-induced hypercalcemia of malignancy (red circles).

PTH: parathyroid hormone.

Data from: Haden ST, Brown EM, Hurwitz S, et al. The effects of age and gender on parathyroid hormone dynamics. *Clin Endocrinol* 2000; 52:329.

60 yo woman – lab evaluation

- Calcium 11.1, Creatinine 0.65, PTH 73 (12-88)
- 24 hour urine Calcium 3.0 mg/dl X 1266 cc = 38 mg / d
- 24 hour urine Creatinine 118 mg / dl X 1266 = 1481 mg / d

60 yo woman - differential diagnosis

- Primary hyperparathyroidism
- Hydrochlorothiazide causing hypercalcemia
- Familial hypocalciuric hypercalcemia
- All of the above

Familial hypocalciuric hypercalcemia

- Autosomal dominant – caused by inactivating mutations in the gene for calcium-sensing receptor (CaSR or CaR)
- Parathyroid gland is less sensitive to calcium, higher calcium concentration is required to reduce PTH.
- Kidney – this leads to increase in tubular calcium and magnesium reabsorption
- Benign natural history
- Parathyroidectomy does not cure disorder

Differentiating PHP from FHH

- PHP – 10% will have "normal PTH" and FHH – 15-20% will have elevated PTH
- Other causes of low calcium excretion – vitamin D deficiency and/or very low calcium intake, thiazide diuretics, lithium
- Ca/Cr clearance ratio – $(24\text{h ur calcium} \times \text{serum creat}) / (\text{serum Ca} \times 24\text{ h ur creat})$
- Ca/Cr ratio < 0.01 in FHH ($>80\%$) and PHP ($<20\%$ most with vit D def)
- Ca/Cr ratio >0.02 essentially excludes FHH
- Ca/Cr ratios $0.01-0.02$ may benefit from genetic testing for FHH

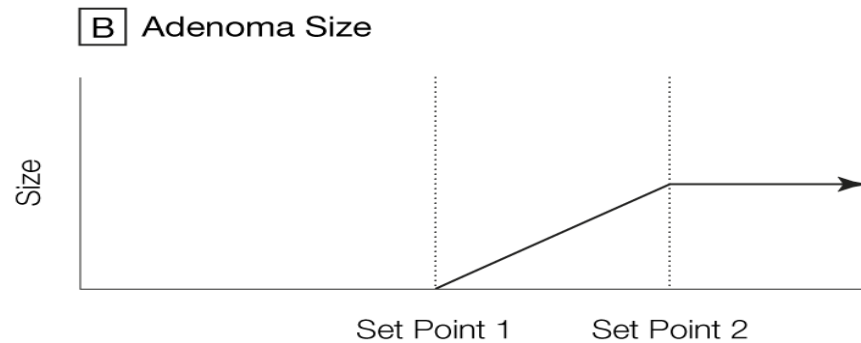
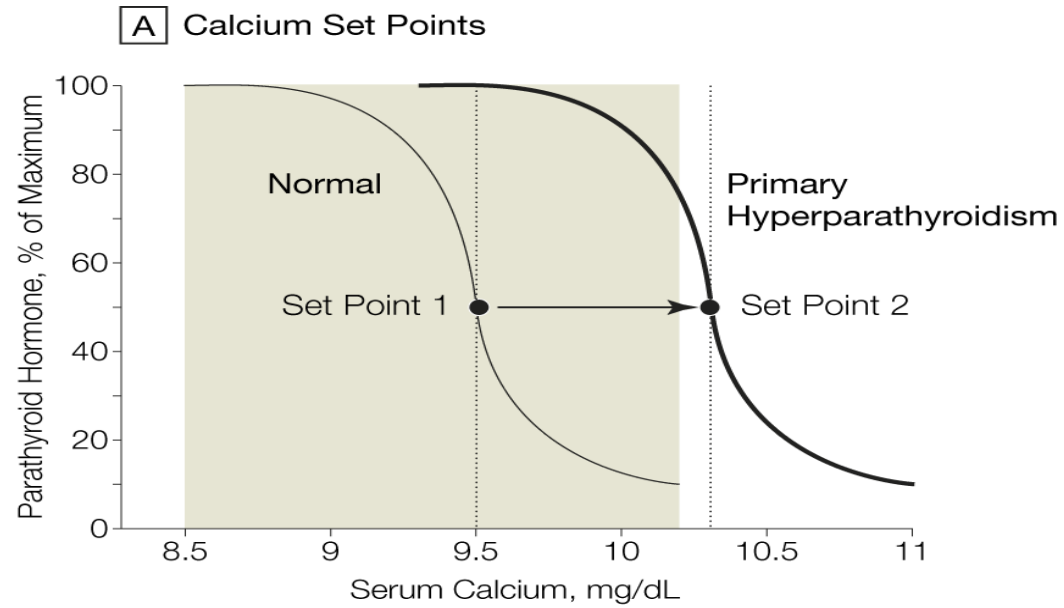
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- Repeat labs off HCTZ – calcium 10.4, PTH 110, 24 hr urine calcium 158 mg / day, 24 hr urine creatinine 1566 mg / day
- Ca/Cr clearance ratio = $(158 \times 0.65) / (1566 \times 10.4) = 0.006$
- Previous serum calcium 2012 9.5; 2011 9.4; 2009 9.6

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Figure 1. Schematic Diagram of Calcium Set Points in Healthy Individuals Compared With Individuals With Primary Hyperparathyroidism and Hypothetical Relationship to Parathyroid Adenoma Size



What are the target organ effects of PHP?

- Bone loss, nephrolithiasis / renal failure, psychiatric / cognitive, increased mortality
- Nephrolithiasis / renal failure, psychiatric / cognitive, no change in mortality, improvement in bone – fewer fractures
- Bone loss, nephrolithiasis / renal failure, psychiatric / cognitive, no change in mortality
- None of the above, “its all too confusing”

PHP and Bone

- Osteitis Fibrosa Cystica – severe hyperparathyroidism



PHP and Bone

- Osteoporosis – commonly seen
- Parathyroid hormone – main effect on cortical bone (radius) increasing fracture risk slightly, less effect on trabecular bone (spine)
- Hyperparathyroidism is associated with about 50% increase in bone turnover – the loss of cortical bone is more marked than increase in trabecular bone
- Therapeutically PTH injected daily – stimulates new bone formation and leads to increased bone mineral density and decreased fracture risk

PHP and kidney

- Serum creatinine, 24 hr urine calcium, imaging to identify urolithiasis
- 24 hr urine evaluation was not able to predict nephrolithiasis in PHP in prospective study

PHP and the brain

- Fatigue, weakness, depression and memory problems are associated with PHP
- RTC of surgery versus observation for asymptomatic PHP, 53 patients, post-op difference in SF-36 social function and emotional role functioning ($P < 0.007$ and < 0.012 respectively)

Medical treatment of PHP

- Calcium and in patients with low vitamin D replacement of vitamin D
- Estrogen
- Bisphosphonates for osteoporotic patients
- Cinacalcet

Surgical treatment of PHP

- Cure approximately 95% of cases
- Complications
 - Re-exploration
 - Laryngeal paralysis
 - Hypoparathyroidism
- Benefits of surgery
 - Reduces incidence of nephrolithiasis by 90%
 - Bone mineral density improves by 10% in 10 years
 - Nonspecific symptoms may improve

Indications for surgery PHP - Fourth International Workshop guidelines 2013

- Serum calcium (> upper limit of normal) 1.0 mg/ dl (0.25 mmol/L)
- BMD by DXA: T score < -2.5 or Vertebral fracture
- Creatinine clearance <60 ml/min, 24 hr urine calcium >400 and increased stone risk by biochemical stone risk analysis, presence of nephrolithiasis
- Age <50
- Surgery is also indicated for whom medical surveillance is neither desired or possible and in patients opting for surgery, in the absence of meeting any guidelines, as long as there are no medical contraindications

60 yo woman with fatigue and PHP

- She was seen by Endocrinologist
- He agrees that this is PHP
- He discussed the diagnosis, prognosis and treatment with the patient and she has elected to see thyroid surgeon to have neck exploration

Surgeon Beware : many pts are misdiagnosed

- 324 pts were referred for PHP surgery
- 265 (82%) diagnosis confirmed
- 60 (19%) were misdiagnosed
 - 54 had secondary hyperparathyroidism
 - 6 had hypercalcemia but no increase in PTH
 - 70% had localization studies and of those 57% suggested positive finding

The correct diagnosis

- Familial Hypocalciuric hypercalcemia 0 cases
- Vitamin D deficiency 37 cases
- Roux-en-Y bypass surgery 4 cases
- Celiac disease 2 cases

Secondary Hyperparathyroidism

- Renal failure
- Decreased calcium intake
- Calcium malabsorption
 - Vitamin D deficiency
 - Bariatric surgery
 - Celiac disease
 - Pancreatic disease
- Renal calcium loss
 - Idiopathic hypercalciuria
 - Loop diuretics
- Inhibition of bone reabsorption
 - Bisphosphonates
 - Hungry bone syndrome

Normocalcemic Primary Hyperparathyroidism

- These cases are found when patients are being evaluated for osteoporosis or nephrolithiasis
- There are no guidelines directed at these patients
- Case series suffer from selection bias towards patients with end organ disease

Surgery at UCH for Primary Hyperparathyroidism

Robert McIntyre, Jr MD

24 years of experience, 100 parathyroid surgeries per year

Primary surgery

Eucalcemia 94%, Hypercalcemia 2%, Hypocalcemia –temp
25%, long term 4%

Secondary surgery

Eucalcemia 75%, Hypercalcemia 11%, Hypocalcemia 14%

Complications rate 1% hoarseness, 0% operative mortality

Surgery at UCH for Primary Hyperparathyroidism

Robert McIntyre, Jr MD

Estimate of the asymptomatic / minimally symptomatic patients who meet the 4th International Workshop guidelines for the management of asymptomatic primary hyperparathyroidism criteria?

50%

Any points that you would like to pass on to an audience of internists:

95% of patients have symptoms based on a careful history and

95% of patients report significant improvement in those symptoms.

Conclusions

- Hypercalcemia is common and the most common causes are primary hyperparathyroidism and malignancy (90%)
- The initial evaluation should include calcium, creatinine, PTH, vit D
- If parathyroid level is elevated then order 24 hr urine calcium and creatinine, consider xray to look for nephrolithiasis / vertebral compression fracture, BMD
- There is no current recommended medical therapy. Correct vitamin D deficiency. Calcium intake of 1,000 mg daily is recommended.

Conclusions

- Surgery is curative in 95% of patients with PHP
- Surgical complications vary by volume of surgeries
 - 3.76% for those < 15 cases annually
 - 1.48% for those > 50 cases annually
- Surgery at UCH equals or exceeds this national data
- Localization studies should be ordered when the decision to proceed to surgery has already been made. They are not helpful in making the diagnosis.