20F With Hypocalcemia

Isabel Casimiro, MD PhD *

5/11/17

* has no relevant financial relationships with any commercial interests.

How to Approach Hypocalcemia?

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- Etiology: Think of factors that influence serum calcium:
  - PTH
  - Vitamin D
  - Calcium ion
  - Phosphate

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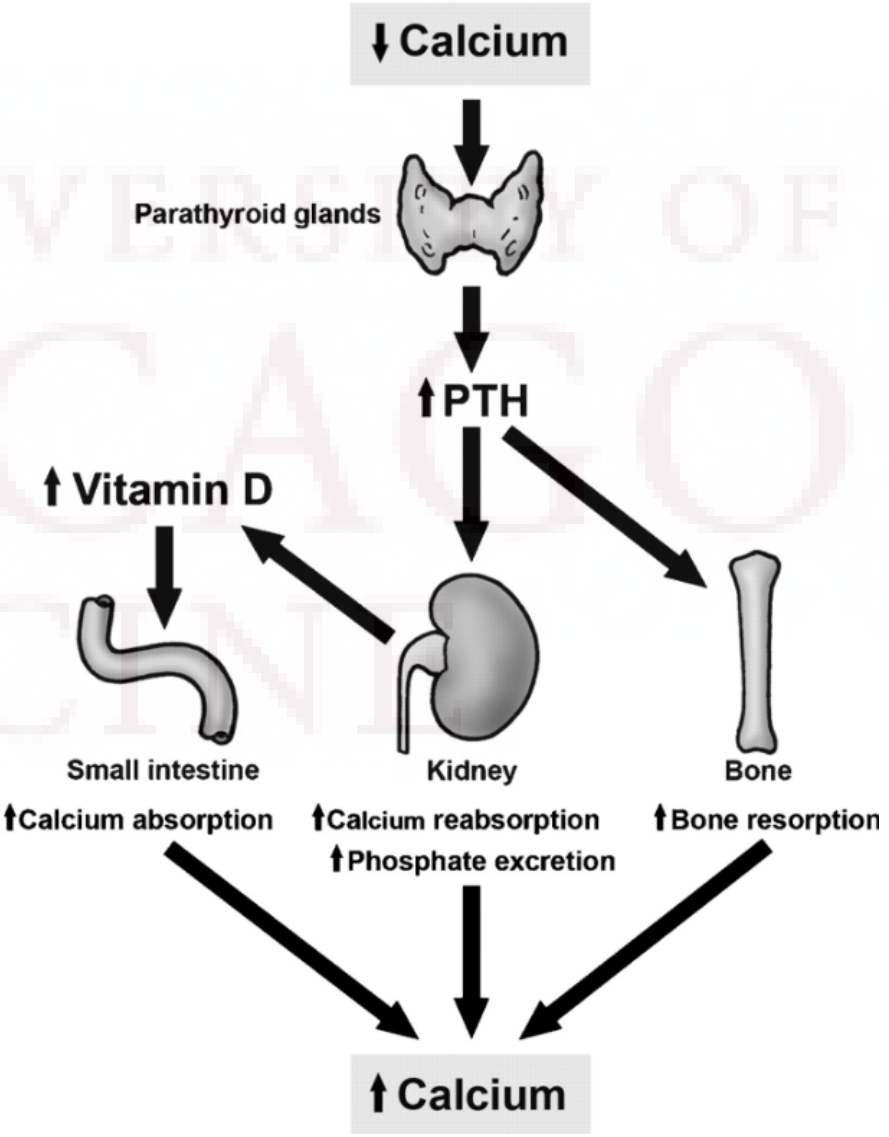
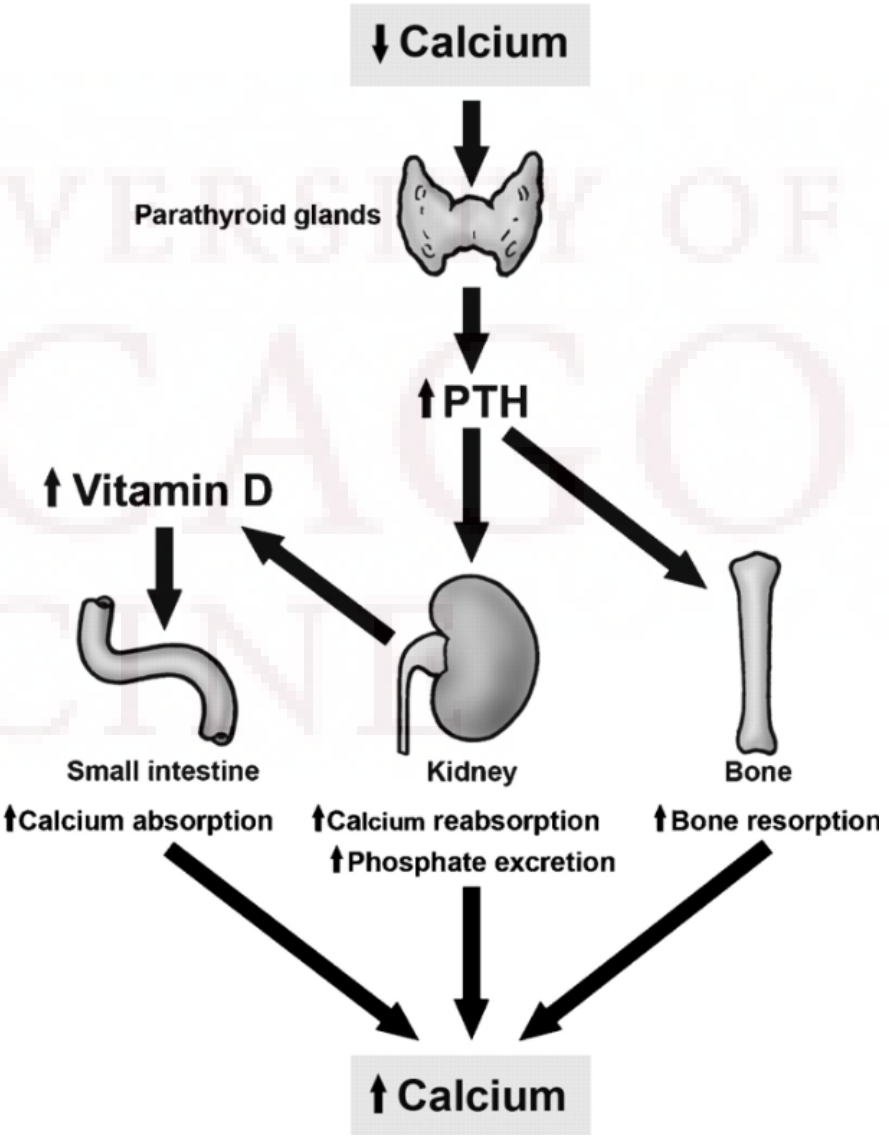
Most often are etiology of hypocalcemia

How does PTH increase calcium levels?



How does PTH increase calcium levels?

- Increased intestinal calcium absorption mediated by increased renal production of 1,25-vit D (calcitriol)
- Decreased urinary calcium excretion due to stimulation of calcium reabsorption in the distal tubule
- Increased bone resorption



Hypocalcemia with Low PTH (Hypopara)

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- Destruction of parathyroid glands
  - Surgical (thyroidectomy, parathyroidectomy, radical neck dissection)
  - Autoimmune (Abs to CaSR, autoimmune polyglandular syndrome)
  - Other (Infiltration of parathyroid gland [hemochromatosis, Wilson's dz, granulomas, metastatic cancer], RT destruction, HIV)
- Abnormal parathyroid gland development
  - Abnormal PTH synthesis
- Altered regulation of PTH
  - Activating mutations of calcium-sensing receptor

Hypocalcemia with High PTH

Hypocalcemia with High PTH

- Vitamin D deficiency or resistance
- CKD
- PTH resistance (impaired PTH action)
  - Missense mutation in PTH
  - Pseudohypoparathyroidism
  - Hypomagnesemia: associated with normal, low & high PTH because it can reduce PTH secretion or cause PTH resistance
- Extravascular deposition
- Loss of calcium from circulation (hyperphosphotemia, tumor lysis syndrome, acute pancreatitis, osteoblastic metastases, acute respiratory alkalosis)
- Sepsis or severe illness
- Surgery

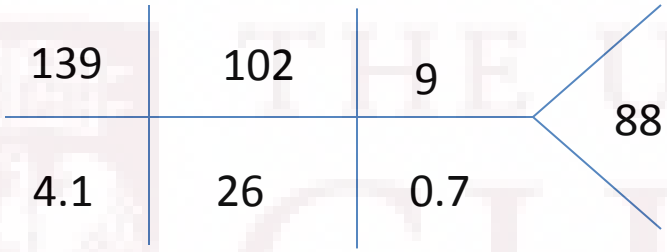
Drugs that can cause Hypocalcemia

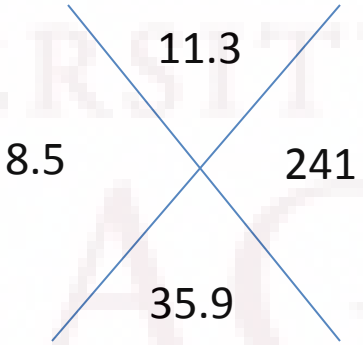
- Calcium chelators (EDTA, citrate, phosphate)
- Inhibitors of bone resorption
  - Bisphosphonates
  - Denosumab
  - Cinacalcet
- Chemotherapy
- Foscarnet (due to conversion of vit D to inactive metabolites
- Fluoride poisoning

Serum PTH Concentrations

- Serum PTH is **reduced** or inappropriately normal in patients with hypoparathyroidism
- Serum PTH is **elevated** in patients with acute or chronic kidney disease, vitamin D deficiency, and pseudohypoparathyroidism
- Serum PTH is **typically normal or low** in patients with hypomagnesemia or autosomal dominant hypocalcemia, a rare disorder characterized by an activating mutation in the calcium-sensing receptor gene

Back to Our Patient

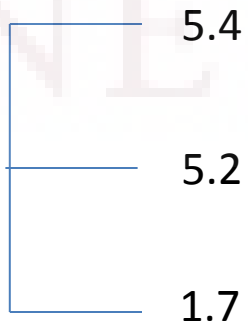




PTH: 884

25-OH vit D: 16

Ionized Ca++ 2.72
Albumin: 4.0
TSH: 1.92
T4: 5.6



Differential for low Calcium in this Pt?

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- Vitamin D deficiency or resistance
- PTH resistance (impaired PTH action)
  - Missense mutation in PTH
  - Pseudohypoparathyroidism

HPI

- 20yo F presenting with numbness and tingling around her face
- Out of meds x 2 months due to insurance issues
- Also with abdominal pain x 2 days

PMH

- Asthma
- Pseudohypoparathyroidism
- Vitamin D deficiency

FH

- Mat GM: DM
- No FH of hypocalcemia or PTH mutations

Meds

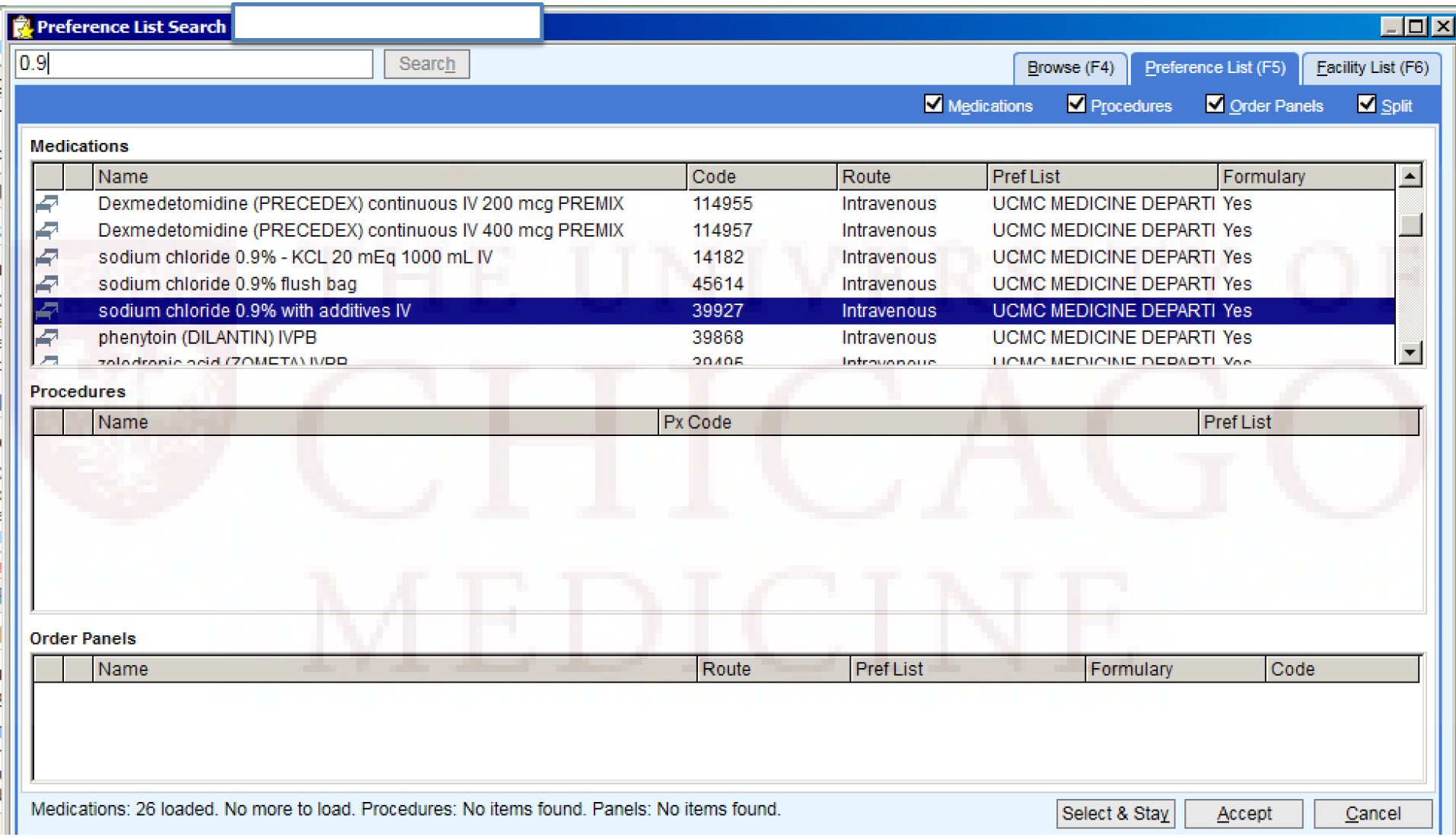
- Calcitriol 0.5 mcg x 8 caps BID
- Tums 750mg x 6 tabs QID
- HCTZ 12.5mg Qd
- Magox 400mg BID

SH

- Lives with GM, works at McDonalds. Has no health insurance currently. No tobacco or EtOH.

Recommendations to Team

- Initiate calcium drip to corrected calcium >7
- How to order calcium gtt??


Preference List Search
0.9
Search
Browse (F4)
Preference List (F5)
Facility List (F6)
Medications
Procedures
Order Panels
Split
Medications
Name
Code
Route
Pref List
Formulary
Dexmedetomidine (PRECEDEX) continuous IV 200 mcg PREMIX
114955
Intravenous
UCMC MEDICINE DEPARTI
Yes
Dexmedetomidine (PRECEDEX) continuous IV 400 mcg PREMIX
114957
Intravenous
UCMC MEDICINE DEPARTI
Yes
sodium chloride 0.9% - KCL 20 mEq 1000 mL IV
14182
Intravenous
UCMC MEDICINE DEPARTI
Yes
sodium chloride 0.9% flush bag
45614
Intravenous
UCMC MEDICINE DEPARTI
Yes
sodium chloride 0.9% with additives IV
39927
Intravenous
UCMC MEDICINE DEPARTI
Yes
phenytoin (DILANTIN) IVPB
39868
Intravenous
UCMC MEDICINE DEPARTI
Yes
Procedures
Name
Px Code
Pref List
Order Panels
Name
Route
Pref List
Formulary
Code
Medications: 26 loaded. No more to load. Procedures: No items found. Panels: No items found.
Select & Stay
Accept
Cancel

sodium chloride 0.9% 1,000 mL with calcium gluconate 11 g ✓ Accept ✕ Cancel

Route: Intravenous | Intravenous

Frequency: CONTINUOUS | ONCE | CONTINUOUS

For: ◯ Hours ◉ Days

Starting: 5/9/2017 | Today | Tomorrow | At: 2200 | Show Additional Options

Starting: **Today 2200** **Until Discontinued**

Scheduled Times: Hide Schedule

5/9/17 2200

Admin. Inst.: Click to add text

Note to Pharmacy (F6): (300 char max.) Click to add text

Additives (Selection Required) ✚ Add

- ☐ potassium chloride
- ☐ MVI with vitamin K
- ☐ folic acid
- ☐ thiamine
- ☑ calcium gluconate 11 g

Base (Selection Required)

◉ sodium chloride 0.9% 1,000 mL | 500 mL | 1,000 mL

Phase of Care:

▸ Additional Order Details

Next Required | Link Order ✓ Accept ✕ Cancel

sodium chloride 0.9% 1,000 mL with calcium gluconate 11 g

Accept Cancel

Route: Intravenous | Intravenous

Frequency: CONTINUOUS | ONCE | CONTINUOUS

For: Hours Days

Starting: 5/9/2017 Today Tomorrow At: 2200 Show Additional Options

Starting: **Today 2200** **Until Discontinued**

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5/9/17 2200

Admin. Inst.: Click to add text

Note to Pharmacy (F6): (300 char max.) Click to add t

Additives (Selection Required) Add

- [ ] potassium chloride
- [ ] MVI with vitamin K
- [ ] folic acid
- [ ] thiamine
- [x] calcium gluconate

Add Addit

11g of 100mg/mL solution of calcium gluconate in 1L NS = 1mg/mL solution

Can start at 50cc/hr (0.5-1.5mg/kg/hr) titrate to achieve corrected Ca >8

Base (Selection Required)

- [x] sodium chloride 0.9% 1,000 mL | 500 mL | 1,000 mL

Phase of Care:

Additional Order Details

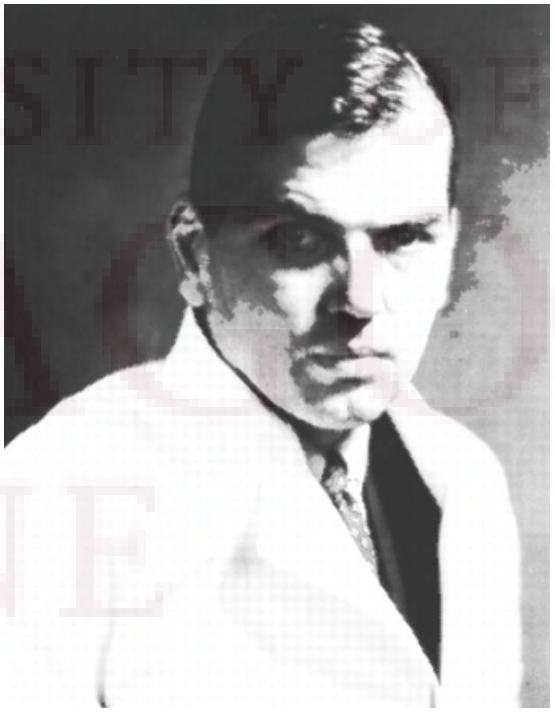
Next Required | Link Order | Accept | Cancel

End Organ Resistance to PTH: AKA Pseudohypoparathyrodism

- Characterized by: hypocalcemia, hyperphosphatemia, elevated PTH concentrations
- Caused by mutations and/or epigenetic changes at the complex GNAS locus on chromosome 20q13.3

Pseudohypoparathyroidism (PHP)

- Term coined by Fuller Albright & his colleagues in 1942 to describe 3 patients who presented with seizures, hypocalcemia, and hyperphosphatemia

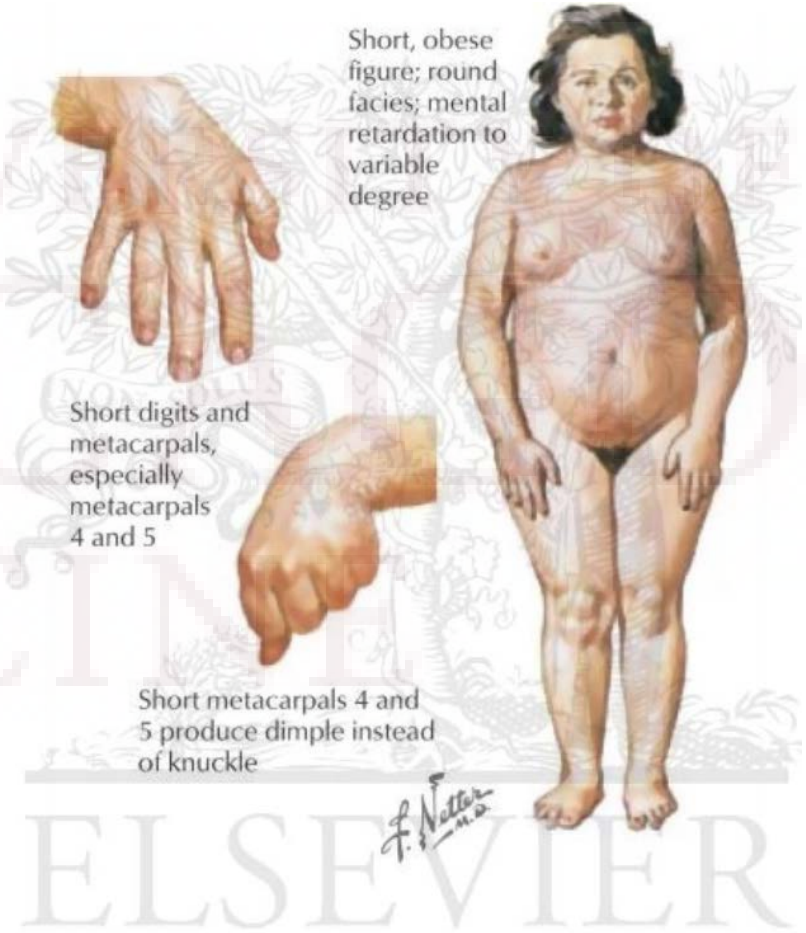


- Repeated injections of parathyroid extracts failed to improve serum calcium or induce increase in urinary phosphate

- Albright & colleagues concluded that their patients were resistant to PTH rather than PTH deficient

Pseudohypoparathyroidism

- Additional characteristics of some Pts with PHP include:
  - Short stocky build
  - Round face
  - Early onset obesity
  - Ectopic inramembranous calcifications
  - Brachydactyly
  - Neurodevelopmental abnormalities



- Refrred to as Albright hereditary osteodystrophy (AHO)

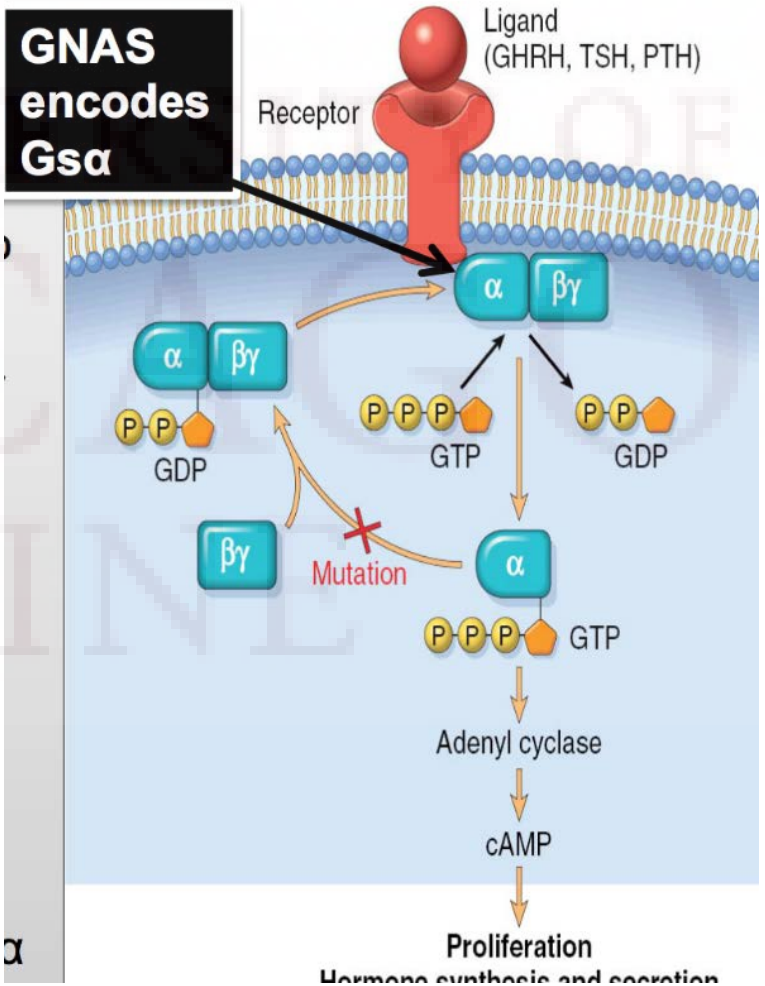
Pseudopseudohypoparathyrodism

- Decade later Albright described a Pt with typical AHO features but normal serum calcium & phosphate
  - Named this disorder: pseudopseudohypoparathyroidism (PPHP)

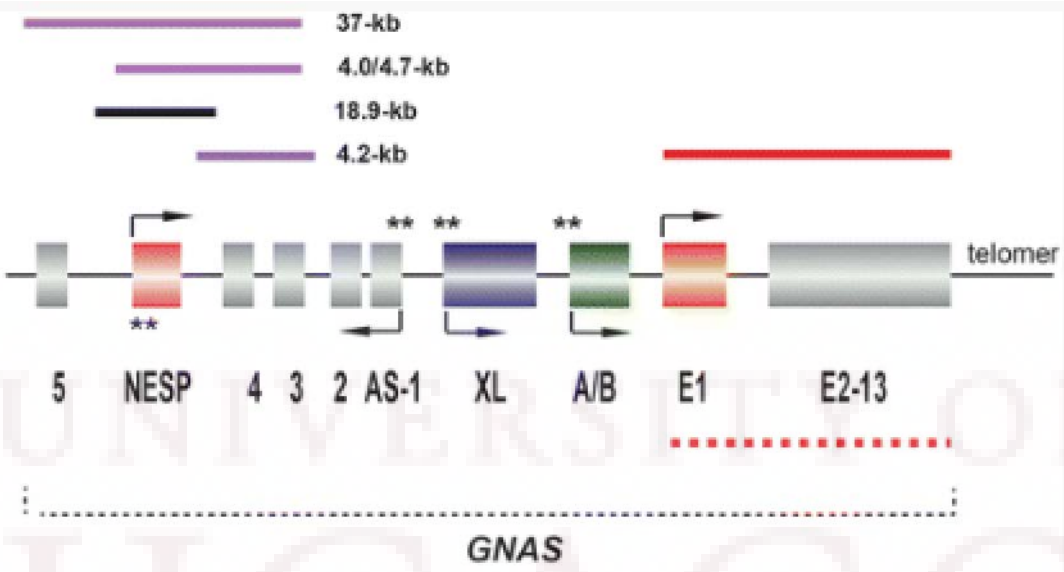
- 1980s: Activity of guanine nucleotide regulatory protein (Gs〈) in RBC membranes from PHP pts was reduced to 50% of controls
  - Reduction in Gs〈 activity also reported for RBC membranes from Pts with PPHP
  - Pts with PHP but no AHO had normal Gs〈 activity
  - Classification as PHP type 1a or type 1b

GNAS

- GNAS gene (chr 20) that encodes Gs〈 that is coupled to PTH receptor (& other hormone receptors)
- Inability to activate adenyl cyclase upon the binding of PTH to its receptor
- Activation required for signal transduction that produces end organ response to PTH
- Gs〈 from tissues like RPT, thyroid, gonads, pituitary, BAT, CNS come from maternal allele



Types of PHP

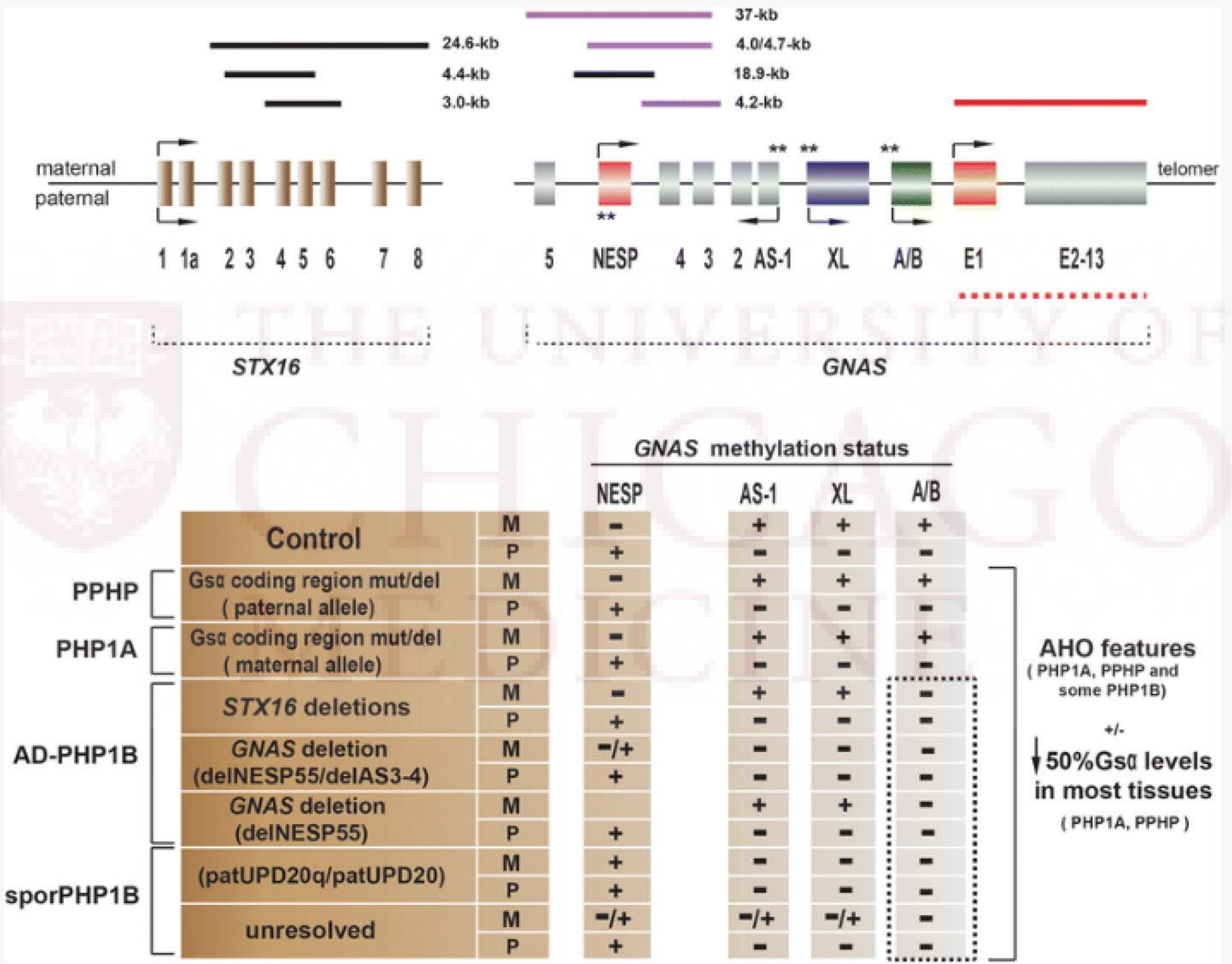


- Type 1A: Autosomal dominant LOF mutation in GNAS1; Caused by heterozygous inactivating mutations involving the **maternal** GNAS exons 1-13 (solid red line)
  - Biochemical abnormalities (PTH resistance)
  - Developmental abnormalities (AHO)
  - Can have resistance to other G proteins (TSH, LH, FSH, GnRH)

- PPHP: Same or similar mutations of GNAS of **paternal** allele (dashed red line)
  - Typically no lab abnormalities
  - Some or all AHO features

Types of PHP

- Type 1B: Autosomal dominant; heterozygous maternal deletions in regulatory elements of GNAS or STX16 (epigenetic regulation, LOM of GNAS exons);
  - PTH resistance in renal proximal tubules
  - No AHO features
- Type 1c: mutations that affect coupling of G protein to the PTH receptor (phenotypically similar to PHP Type 1A)
- Type 2: Normal or elevated cAMP in response to PTH administration but without a concomitant increase in phosphate excretion; Do not have features of AHO


37-kb
24.6-kb
4.0/4.7-kb
4.4-kb
18.9-kb
3.0-kb
4.2-kb
maternal
paternal
telomer
1 1a 2 3 4 5 6 7 8
5 NESP 4 3 2 AS-1 XL A/B E1 E2-13
STX16
GNAS
GNAS methylation status
NESP AS-1 XL A/B
Control
M - + + +
P + - - -
PPHP
Gsα coding region mut/del (paternal allele)
M - + + +
P + - - -
PHP1A
Gsα coding region mut/del (maternal allele)
M - + + +
P + - - -
AD-PHP1B
STX16 deletions
M - + + -
P + - - -
GNAS deletion (delNESP55/delAS3-4)
M -/+ - - -
P + - - -
GNAS deletion (delNESP55)
M + + -
P + - - -
sporPHP1B
(patUPD20q/patUPD20)
M + - - -
P + - - -
unresolved
M -/+ -/+ -/+ -
P + - - -
AHO features
(PHP1A, PPHP and some PHP1B)
+/-
50%Gsα levels in most tissues
(PHP1A, PPHP)

Prior Hx of this Problem

- Diagnosed with pseudohypoparathyroidism in 2003 during hospitalization for hypocalcemia seizure at age 7
- Hx of frequent hospitalizations for profound hypocalcemia & tetany due to noncompliance
- Refill pattern investigation in 2011 showed she was taking her pills 30-50% of the time
- Multiple ED/admissions for hypocalcemia since 2015

Recommendations

- Start calcium drip until calcium reaches 7-8, then start PO calcium 2500mg calcium carbonate TID
- Continue calcitriol 3mcg BID
- Continue HTCZ
- Consult SW regarding f/u plan/obtaining meds; F/u made at Cook County

Treatment

- Similar to treatment of hypocalcemia caused by other forms of hypoparathyroidism
- However, Pts with PHP rarely develop hypercalciuria with calcium & vit D therapy
- Goal of treatment with calcium and vit D is to maintain normocalcemia
- May require screening for other endocrinopathies (TSH resistance)
- Typical starting dose calcitriol 0.25mcg BID & 1-2g elemental calcium daily (in divided doses)

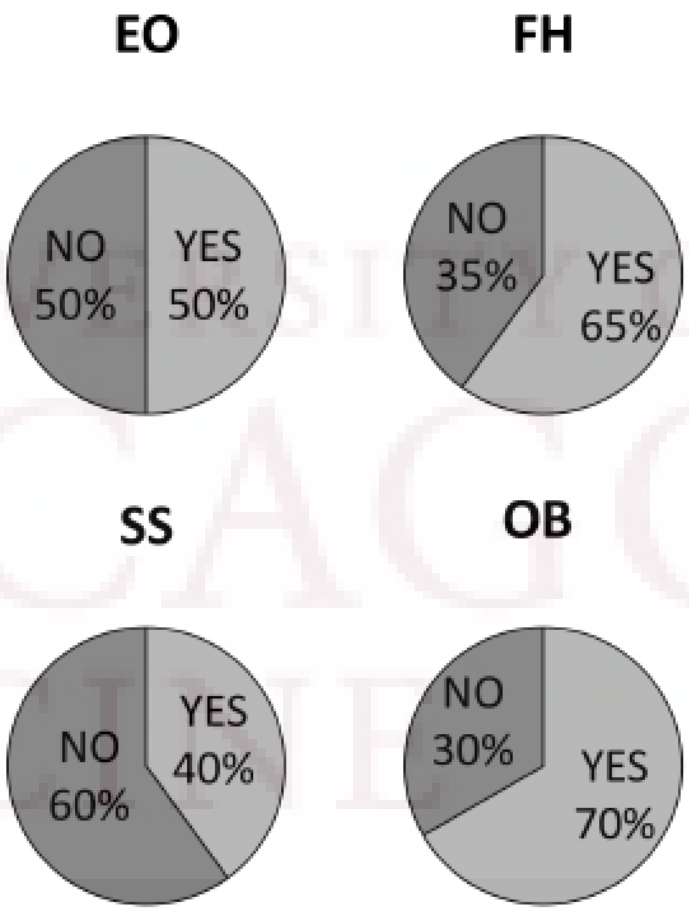
Progressive development of PTH resistance in patients with inactivating mutations on the maternal allele of *GNAS*

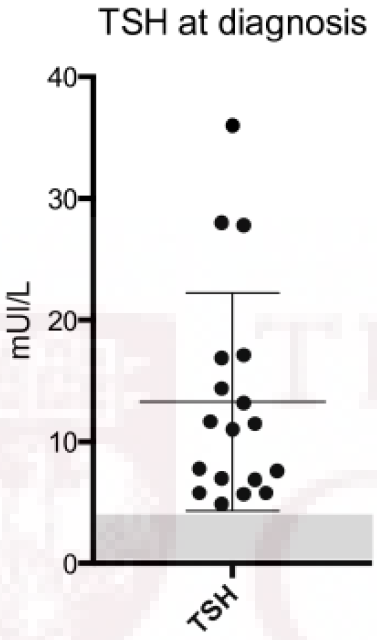
Alessia Usardi, Asmaa Mamoune, Elodie Nattes, Jean-Claude Carel, Anya Rothenbuhler, Agnès Linglart

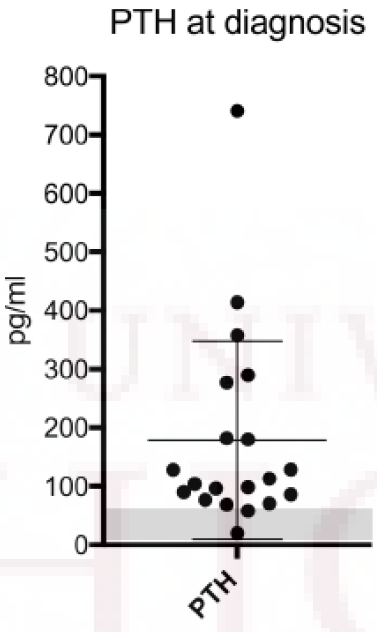
J Clin Endocrinol Metab jc.2016-3544. **DOI:** https://doi.org/10.1210/jc.2016-3544
Published: 21 February 2017 **Article history** ▾

- Diagnosis of Type 1a PHP relies on discovering PTH resistance when children present with AHO features
- Patients do not present with hypocalcemia or elevated PTH until after first years of life
- Objective of this study: To assess PTH resistance over time in 20 patients with Type 1A PHP

Affected patients with ectopic ossifications, family history, short stature or obesity

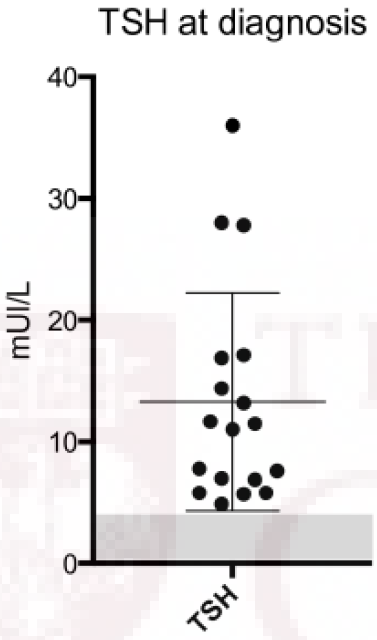


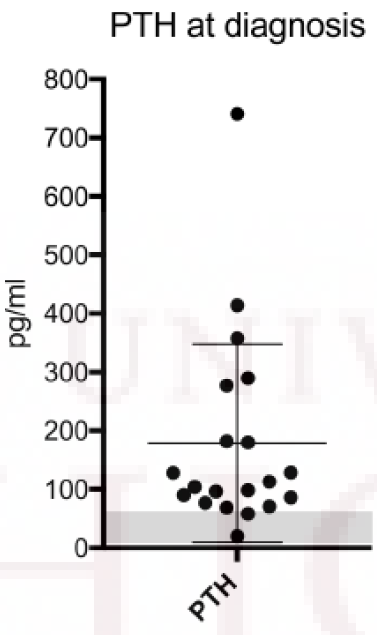




All patients had abnormally high levels of TSH at diagnosis or study start

Not all patients had elevated PTH (2/20 nml, 8/20 modestly increased)





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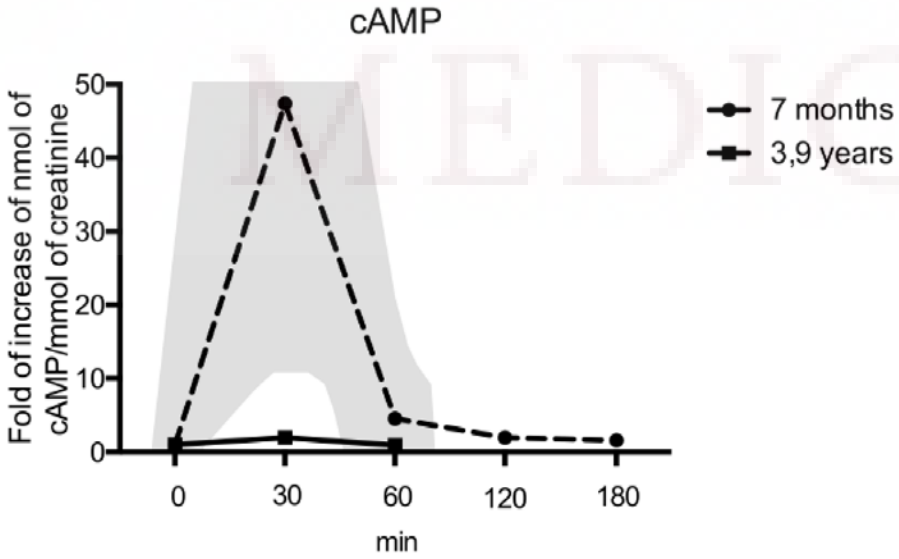
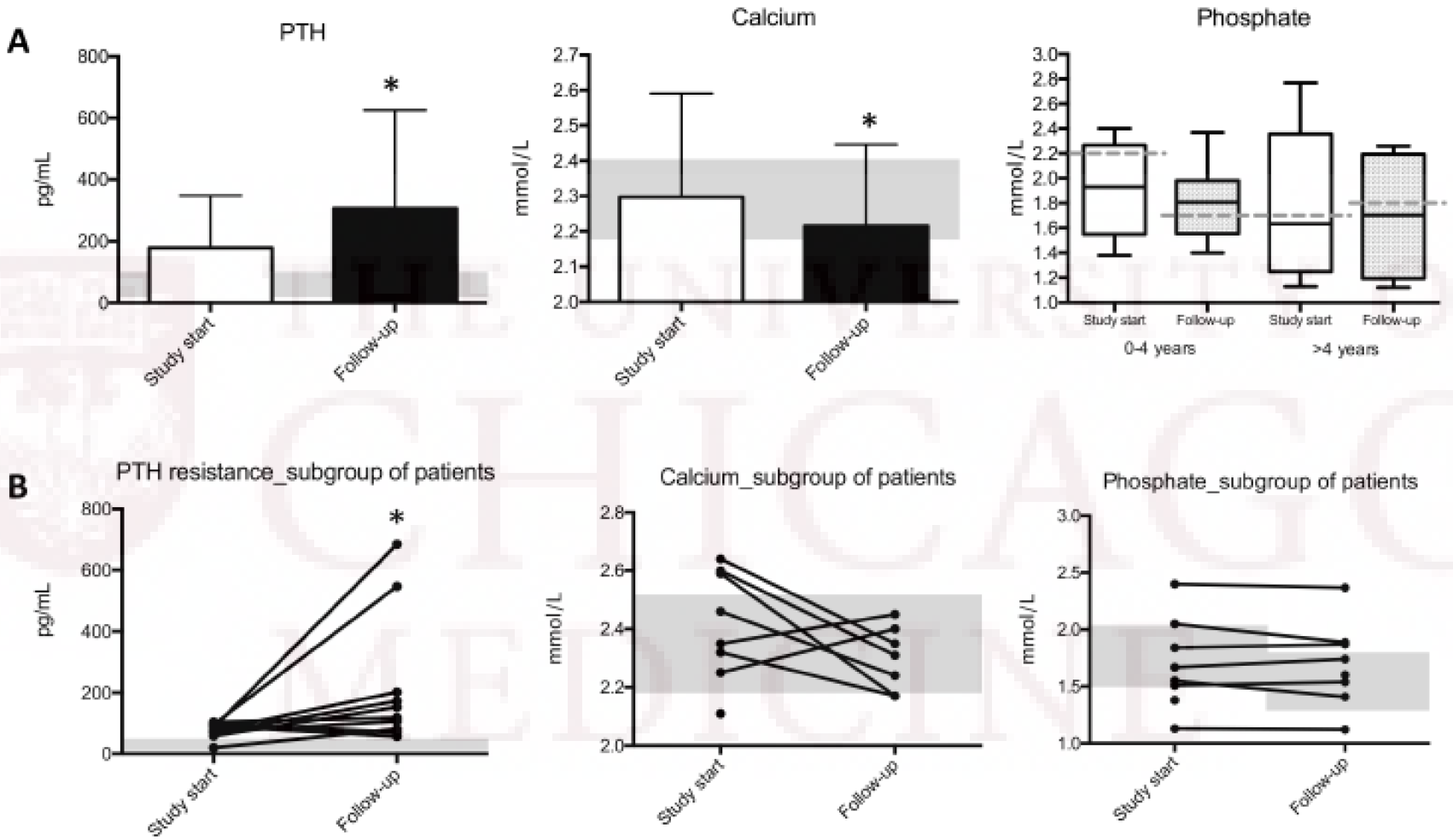


One Pt with PHP Type 1a (EO in neck), showing normal cAMP rise at 7 mos, and blunted response to PTH infusion test at age 3.9 yrs



Values of PTH increased and calcium levels decreased at f/u compared to study start. Phosphate levels remained normal

Conclusions

- PHP first coined by Fuller Albright & colleagues in 1942 to describe Pts that presented with seizures, hypocalcemia, and hyperphosphatemia consistent with diagnosis of hypoparathyroidism found to be resistant to PTH rather than deficient
- Additional features of these patients can include: short stocky build, early onset obesity, ectopic intramembranous calcifications, bracydactyly, & neurodevelopment abnormalities (referred to as Albright hereditary osteodystrophy AHO)
  - Seen in Type 1a & PPHP
- PHP is caused by mutations/epigenetic changes at the GNAS locus coding for the alpha subunit of stimulatory G protein (Gs〈)
- Resistance toward other hormones (including TSH) can occur as well, but resistance to PTH in the PRT is the most prominent abnormality
- In Type 1a PHP patients, calcium levels may be normal at time of diagnosis but significantly decrease over time; PTH resistance profile usually seen in a 2 year period

References

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Objectives

- Discuss differential for hypocalcemia
- Learn about genetic mutations that can lead to PTH resistance

- 1 g calcium carbonate = 400mg elemental calcium