Hypercalcaemia: A diagnostic Challenge

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Case: 44 Male

- Elect. admission for OGD: epigastric pain
- Finding of severe HTN with sig. renal impairment, OGD was cancelled
- Also found to have aCa 3.19 mmol/l
- PMH : Episcleritis, HTN, Gout, PTSD
- Meds: Amlodipine, Allopurinol, Olanzapine
- Retired Prison officer

- FH: Not significant
- Physical Exam: Not significant
- Treatment: Anti hypertensives ,IV Fluids and Bisphosphonates
- Renal Review: Likely HTN nephrosclerosis
- Further work up requested
- Endo. Team, Re: hypercalcaemia
- High Cal.+ severe HTN

  Unifying Diagnosis ???

Diagnostic Work Up

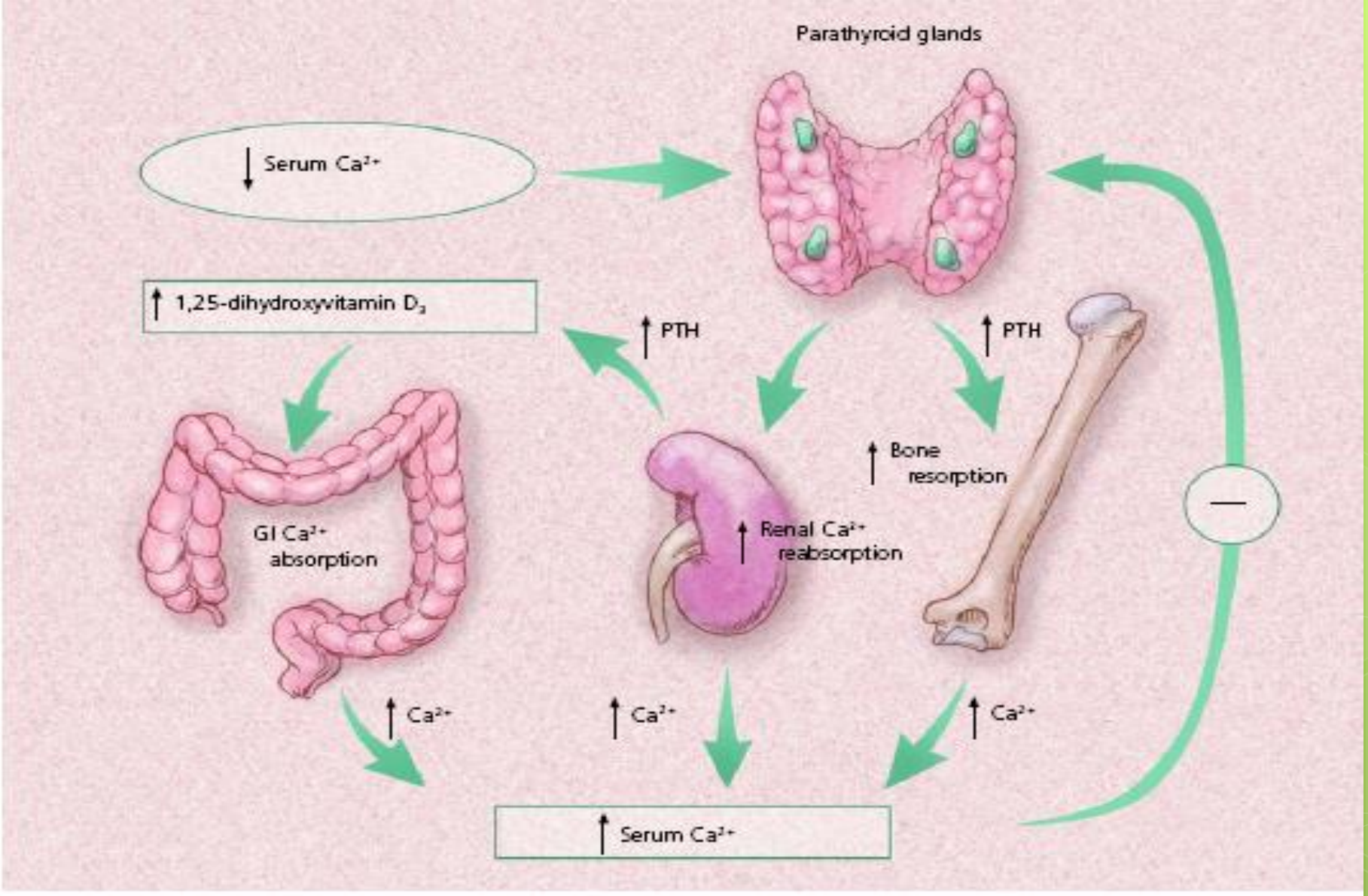


FIGURE 1. Parathyroid gland action. Low circulating serum calcium (Ca^{2+}) concentrations stimulate the parathyroid glands to secrete parathyroid hormone (PTH), which mobilizes calcium from bones by osteoclastic stimulation. PTH also stimulates the kidneys to reabsorb calcium and to convert 25-hydroxyvitamin D_3 (produced in the liver) to the active form 1,25-dihydroxyvitamin D_3, which stimulates gastrointestinal calcium absorption. High serum calcium concentrations have a negative feedback effect on PTH secretion. (GI = gastrointestinal)

Vit. D intoxication
Teriparatide
Lithium
Thiazide
Milk Alkali Synd.
Hypervitaminosis A

Evaluation of Hypercalcemia

Moans,Bones, Groans,Stones

Hypercalcemia detected

aCa : 2.20-2.60mmol/l

Careful history and physical examination focusing on:
- Clinical features of hypercalcemia (see Table 2)
- Possible causative diseases (see Table 3)
- Possible causative medications, including OTC (see Table 3) → Stop causative medications if possible, and recheck calcium level.

Measure intact PTH level

Suppressed

Symptom-guided malignancy work-up
Solid tumors
- ↑PTHrP: adeno and squamous cancer (e.g., lung tumor)
- ↑Alkaline phosphatase: bone lysis (e.g., breast tumor)

Hematologic malignancies
- Positive myeloma screen: multiple myeloma
- ↑Calcitriol: lymphoma, granulomatous diseases

If malignancy work-up is negative

Test for other endocrinopathies (consider

Thyrotoxicosis, Pheochromocytoma, Adrenal insufficiency

Normal or high

Check 24-hour urinary Ca** level

Low

Familial hypocalciuric hypercalcemia

Normal or high

Primary or tertiary hyperparathyroidism

Sporadic/Familial

If surgery indicated (see Table 4)

Consider parathyroid sestamibi scan.

Parathyroidectomy

Clinical Features(Table-2)

- Moans:

Nausea, Vomiting,

Constipation, Abdo. Pain, Pancreatitis, PUD

- Bones:

Bone pains,

Osteoporosis

- Stones:

Nephrolithiasis,

Nephrogenic DI, Polyuria

- Groans:

Lethrgy,Fatigue,

Confusion, Muscle aches

- Cardiovascular:

HTN, Cardiac arrhythmias sec. to short QT interval

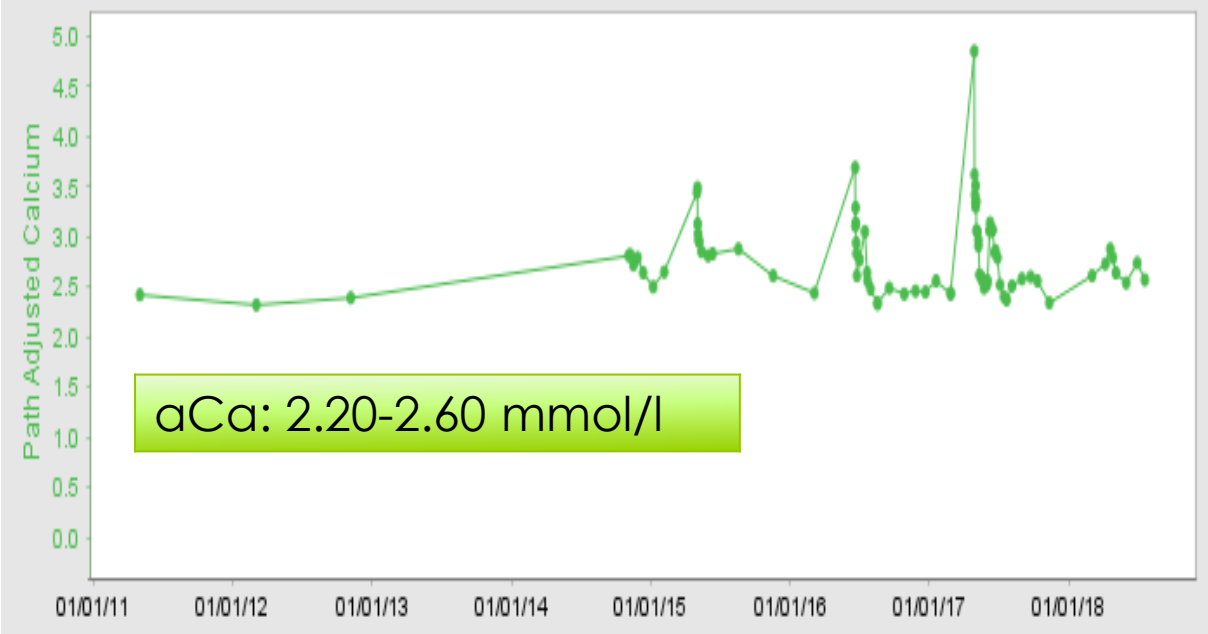
- Others:

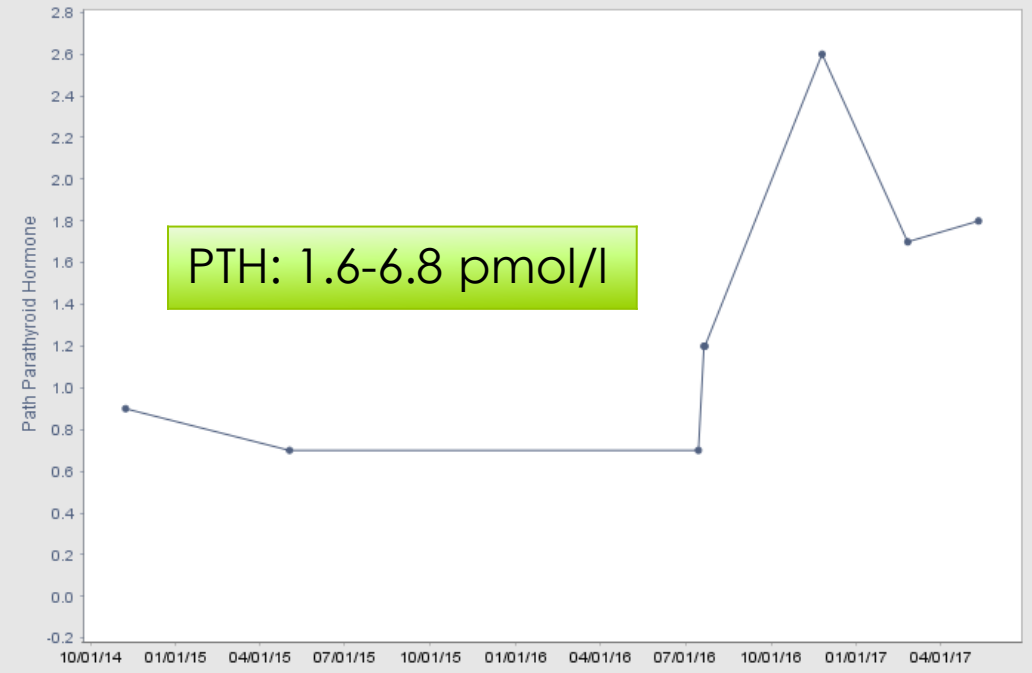
Itching, Keratitis, Episcleritis

Miscellaneous

- Prolonged Immobilization
- Paget's Disease
- Hypophosphatasia
- Rhabdomyolysis

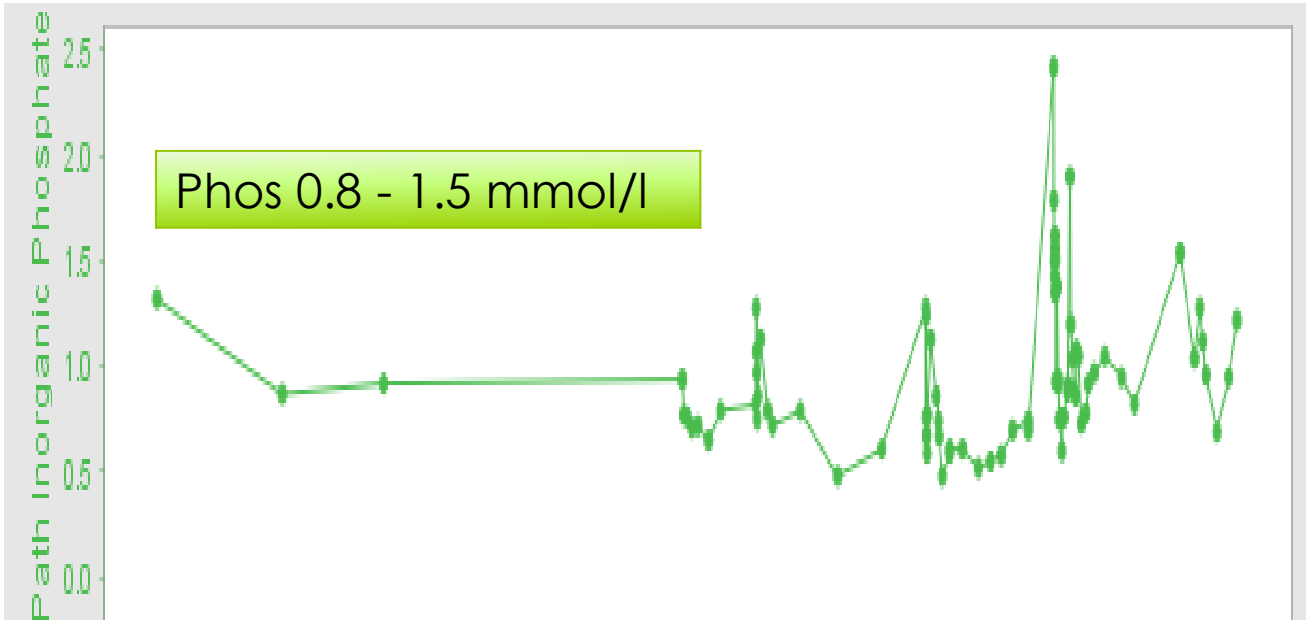
Diagnostic Work Up




PTH: 1.6-6.8 pmol/l
Path Parathyroid Hormone
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
10/01/14
01/01/15
04/01/15
07/01/15
10/01/15
01/01/16
04/01/16
07/01/16
10/01/16
01/01/17
04/01/17


Path Total Vitamin D
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
11/01/14
12/01/14
01/01/15
02/01/15
03/01/15
04/01/15
05/01/15
06/01/15
07/01/15
08/01/15
09/01/15
10/01/15
11/01/15
Vit D 50-150nmol/l


Path Angiotensin Converting Enzyme
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
10/01/14
01/01/15
04/01/15
07/01/15
10/01/15
01/01/16
04/01/16
07/01/16
10/01/16
01/01/17
04/01/17
ACE: 15-55 iu/l


Path Inorganic Phosphate
2.5
2.0
1.5
1.0
0.5
0.0
Phos 0.8 - 1.5 mmol/l

Further Investigations

- Alk. phos: normal ANCA: Negative
- TFTs & Cortisol : Normal
- Fractional excretion of Calcium: 0.063
- 24 hr Urinary Ca. excretion 22.6 (2.5-7.5)
- PTHrP: undetectable
- Urine/Plasma met. & normetanephrines: Normal
- SPEP/UPEP: No abnormal monoclonal bands
- 1- 25 (OH) Vit D: 196pmol/l(Sig. Elevated)
- P1NP 21, Plasma CTX: Normal

- **CT TAP**: No significant abnormality X 2
- **HRCT** : No granulomatous disease/Lymphadenopathy
- **Octreotide Scan** : No evidence of neuroendocrine tumour
- **FDGPET**:Focal area of high intensity FDG activity with in the gastric pylorus
- **OGD**: Gastritis, Bx: Reactive gastritis

Vit. D Related Hypercalcemia

- **Exogenous Vitamin D Toxicity**

Various Preps. Of vitamin D, 25(OH)D, 1,25$(OH)_2$D, analogues such as 1a(OH)D

- **Excessive Production of Vitamin D**

Granulomatous dis.producing1,25$(OH)_2$D

Sarcoidosis, tuberculosis, leprosy, histoplasmosis, candidiasis, Wegener's , Crohn's disease, silicone, paraffin & talc induced granulomatosis.

Lymphomas & malignant lymphoproliferative disease

Congenital disorder: Williams syndrome

- **Reduced degradation of $1,25(OH)_2D$**

Inactivation Mutations in *CYP24A1* gene:

Defective 24 Hydroxylase

Reduced degradation of $1,25(OH)_2D$

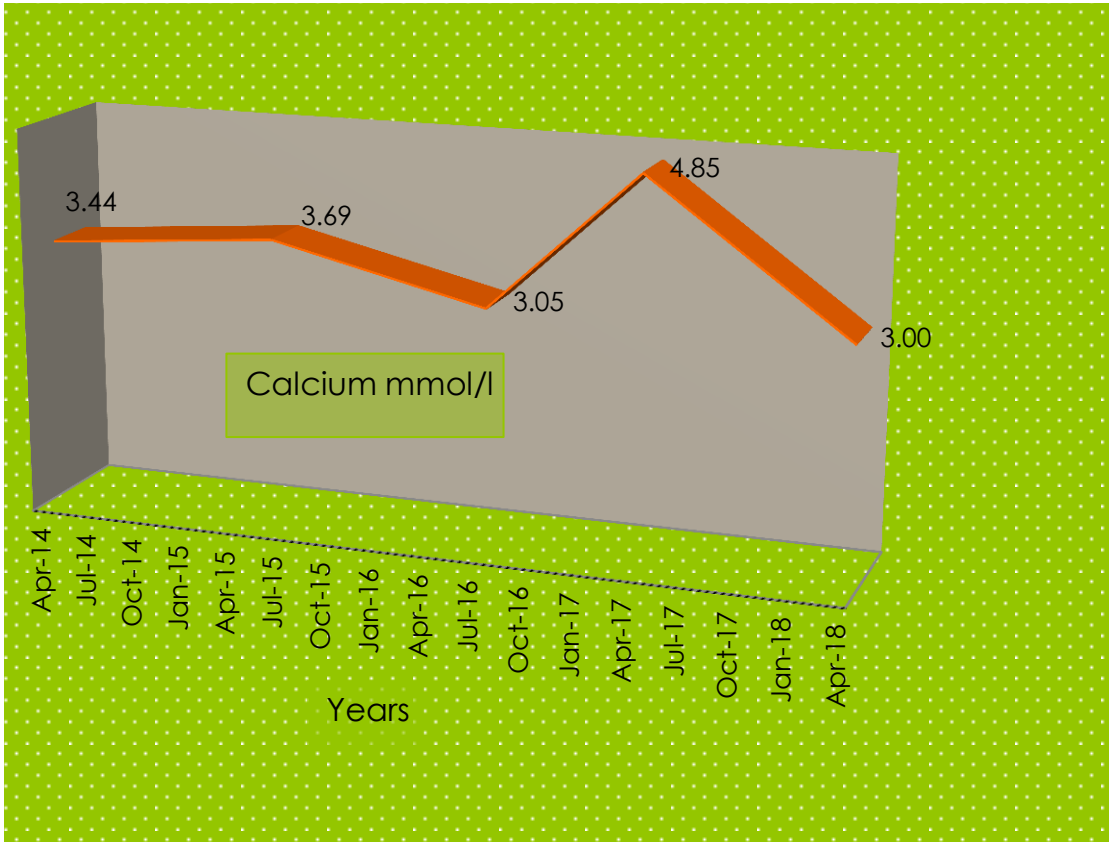
Infantile and adult hypercalcemia

CYP24A1 Mutation

- First described in 2012,almost 100 cases since
- May present with any clinical feature associated with hypercalcaemia
- Additional features described include severe HTN
- Lab. Findings: hypercalcemia, low PTH, and high1,25$(OH)_2$D. 25(OH)D can be low/normal.
- With *CYP24A1* mutations →Low 24,25$(OH)_2$D levels

Vitamin D-Mediated Hypercalcemia: Mechanisms, Diagnosis, and Treatment Peter J. Tebben, Ravinder J. Singh, and Rajiv Kumar

- Exposure to UV rays in summer or tanning bed use can lead to intermittent hypercalcaemia.



PHPT VS Hypervitaminosis D

- The presence of hyperphosphatemia is a clue to the presence of hypervitaminosis D. It occurs as a result of an increase in intestinal and renal phosphate absorption.

- In contrast, patients with primary hyperparathyroidism have hypercalcemia and hypophosphatemia on account of PTH-mediated losses of phosphate in the urine

Treatment of Vit D dependent Hypercal.

- **Emergency**:

severe hypercalcaemia is managed according to standard guidelines

- **Long term**:

1. Low-calcium & vitamin D diet
2. Drugs: Glucocorticoids, loop diuretics, PPI, and antifungals

Glucocorticoids not a desirable long-term solution due to a multitude of toxicities.

Azoles(keto/fluconazole) very affective.

i. Prevent 1 hydroxylation of 25(OH)D.
ii. Caution: P450 enzyme inhibition, can lead to toxicities

Response to Glucocorticoids

- Our patient was started on prednisolone and responded very well
- Weaned off after six months due to neuropsychiatric s/e
- Restarted after 3 months due to very high peak in calcium(4.85)
- Being tapered off again with a view to start antifungal meds.

Case Summary

- Non PTH medicated hypercalcaemia
- Vit D related Hypercalcaemia
- Work up is negative for Malignancy and Granulomatous disorders
- High level of active vit D along with intermittent peaks of Calcium and phosphate specially in summer season point towards CYPT24A1 mutation
- 24,25 hydroxy vit D and genetic testing shall further confirm the diagnosis(Pending)

Emergency management of acute hypercalcaemia in adult patients

SOCIETY FOR ENDOCRINOLOGY GUIDELINES

Jennifer Walsh, Neil Gittoes, Peter Selby

Severity Of Hypercalcaemia

- <3.0 mmol/L: often asymptomatic and does not usually require urgent correction
- 3.0–3.5 mmol/L: may be well tolerated if it has risen slowly, but may be symptomatic and prompt treatment is usually indicated
- >3.5 mmol/L: requires urgent correction due to the risk of dysrhythmia

Corrected/Adjusted Calcium

TCa (mmol/L) + 0.02 (40 (g/L) – albumin)

First-line Treatment

1 Rehydration

- Intravenous 0.9% Saline: 4–6 L in 24 h
- Monitor for fluid overload if renal impairment or elderly
- Loop diuretics : used only, if fluid overload develops. Not effective for reducing serum calcium
- May need to consider dialysis if severe RF

2 Intravenous bisphosphonates

- Zoledronic acid: 4 mg over 15 min
- Pamidronate: 30–90 mg (depending on severity of hypercalcaemia)
- Ibandronic acid: 2–4 mg
- Monitor serum calcium response: will reach nadir at 2–4 days
- Caution: renal impairment

Second-line Treatment

- **Glucocorticoids**

Inhibit (1,25OH)D production

In lymphoma, granulomatous diseases or Vit D toxicity

Prednisolone 40 mg daily

Usually effective in 2–4 days

Treatment under specialist supervision

- **Calcimimetics**: Cinacalcet , (THPT & rarely used in PHPT)
- **Human Monoclonal antibody**: Denosumab
- **Calcitonin:** very quick onset, tachyphylaxis
- **Parathyroidectomy**

Can be considered for acute presentation of primary hyperparathyroidism (poor response to other measures/Pregnancy)

Summary

- History : Medication +OTC Examination: include ECG
- Request PTH and Vit D
- Endocrinology team on board. Further biochemical & radiological investigations
- PHP & Malignancy account for 90% cases
- Severe hypercalcaemia is usually seen in malignancy
- Emergency treatment of Hypercalcaemia remains same irrespective of underlying cause.