CALCIUM DISORDERS

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PARATHYROID DISORDERS

Parathyroid Glands

- Thyroid cartilage (Adam's apple)
- Parathyroid glands
- Trachea (windpipe)
- Carotid artery
- Larynx
- Parathyroid gland
- Thyroid gland

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Regulators of calcium balance

NB!

- PTH
- Vitamin D
- NOT CALCITONIN
The most important questions with calcium abnormalities

For hyper- and hypocalcaemia:
- What is the PTH?
- What is the phosphate?

For hypocalcaemia:
- What is the Vitamin D (25 OH- and 1,25 OH-vit D level)?
- What is the magnesium?

HYPERCALCAEMIA
Case presentation

- Mr GF, 24 year old man
- Single, two children
- Never smoked, alcohol only socially
- Unemployed
- Never worked in mines; grew up in the Western Cape

Presented with:
- Weight loss of >10kg over 8 months
- Chest pains (especially left posterior)
- Coughing
- Weakness, tiredness, depression
- 3 x sputums negative for TB at clinic
- CXR: large mass in his left lung
- Referral to the hospital
On examination:

- Hypertensive (BP 170/100)
- Emaciated
- No significant lymphadenopathy
- Local bony tenderness over left lung posterior
- Areas of tenderness also over right ribs lateral
- Decreased air entry left lower lobe, with basal crepitations
- Clear left ventricular hypertrophy, with 1+ protein in the urine, and gr 2 hypertensive changes of the fundi

Blood results:

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<th>26/6/9</th>
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<td>Na</td>
<td>143</td>
<td>139</td>
<td>141</td>
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<td>135-147</td>
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<td>K</td>
<td>3.7</td>
<td>5.0</td>
<td>4.2</td>
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<td>3.3-5.3</td>
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<tr>
<td>Cl</td>
<td>108</td>
<td>106</td>
<td>107</td>
<td></td>
<td>99-113</td>
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<tr>
<td>Urea</td>
<td>6.4</td>
<td>6.5</td>
<td>7.6</td>
<td>7.7</td>
<td>2.6-7.0</td>
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<tr>
<td>Creat</td>
<td>132</td>
<td>140</td>
<td>158</td>
<td>141</td>
<td>60-120</td>
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</table>
- Normal FBC
- Normal TFT
- HIV negative
- Glucose: 4.8
## HYPERCALCAEMIA

- Hyperparathyroidism is the most common cause in adults (outpatients)
- Second most common cause is malignancy (especially if Ca > 3.25mmol/L) (inpatient: commonest cause)
- Hyperparathyroidism and cancer account for 90% of cases
- First confirm hypercalcaemia before workup
- Hypercalcaemia in an asymptomatic adult is usually due to hyperparathyroidism

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<td>2.87</td>
<td>2.90</td>
<td>3.00</td>
<td>2.05-2.56</td>
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<td>Alb</td>
<td>37</td>
<td>39</td>
<td>44</td>
<td>35-52</td>
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<td>Corr Ca</td>
<td>2.93</td>
<td>2.92</td>
<td>2.92</td>
<td>2.05-2.56</td>
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<td>Mg</td>
<td>0.67</td>
<td>0.63</td>
<td>0.71</td>
<td>0.65-1.10</td>
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<tr>
<td>Phosph</td>
<td>0.68</td>
<td>0.73</td>
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<td>0.80-1.40</td>
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NB!

- After confirming hypercalcaemia:

**Is PTH high or low?**

CAUSES OF HYPERCALCAEMIA

- **PTH-mediated (PTH high or inappropriately N):**
  - Primary hyperparathyroidism
    - solitary adenomas
    - hyperplasia
  - Familial
    - Familial hypocalciuric hypercalcaemia
    - Multiple endocrine neoplasia (MEN-I, IIA)
  - Tertiary hyperparathyroidism
- **PTH-independent (PTH low):**
  - Hypercalcaemia of malignancy
  - Vitamin D intoxication
  - Chronic granulomatous diseases
  - Medications (e.g., thiazide diuretics, lithium)
  - **Endocrine conditions:** - hyperthyroidism
    - phaeochromocytoma
    - acromegaly
    - adrenal insufficiency
  - Other: milk alkali syndrome, immobilization, parenteral nutrition
Possibilities in our patient

We thought he had most likely:

- Hypercalcaemia of malignancy
  = Secondary to lung tumour (? sarcoma)

**HYPERCALCAEMIA OF MALIGNANCY**

- Relatively common in malignancy (10-20% of cases)
- NB: usual scenario: low PTH
Mechanisms of hypercalcaemia in malignancy

- Most important 3 mechanisms:

1. Osteolytic metastases
2. Parathyroid hormone-related protein (PTHrP)
3. Tumour production of calcitriol (active vitamin D)

For completeness sake…

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<td>PTH</td>
<td>70.9</td>
<td>149.8</td>
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<td>1.2 - 8.5 pmol/l</td>
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<tr>
<td>Creat clear</td>
<td>61.2</td>
<td>56.6</td>
<td>85-125</td>
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Parathyroid scan

Working diagnosis

Hypercalcaemia due to a combination of:

- Local infiltration by a lung tumour (?sarcoma) with osteolytic bone metastases
- Coexisting primary hyperparathyroidism due to a parathyroid adenoma
HYPERPARATHYROIDISM

- PTH increases the serum calcium (and decreases serum phosphate) through different mechanisms
- Primary hyperparathyroidism: ↑ PTH, leads to ↑ calcium, ↓ phosphate
- Usually caused by an adenoma, or diffuse hyperplasia of the parathyroids
PRIMARY HYPERPARATHYROIDISM

- Generalized disorder of calcium, phosphate, and bone metabolism due to ↑ PTH
- Symptoms vary greatly, from:
  - asymptomatic hyperparathyroidism; to:
  - hypercalcaemic parathyroid crisis
- Often coincidental finding
- Annual incidence = 0.2% in patients > 60; estimated prevalence = ≥ 1%

Symptoms and signs

- Patients can have symptoms of hypercalcaemia
- Ca < 2.9: often asymptomatic
- > 2.9-3: symptoms more common
- > 3.2: calcification in kidneys, skin, vessels, lungs, heart, stomach; renal insufficiency
- > 3.7-4.5: = medical emergency; coma, cardiac arrest
Symptoms and signs (cont)

- “Stones”
- “Bones”
- “Psychic moans”
- “Abdominal groans”

“Stones”:
- renal stones
- nephrocalcinosis
- polyuria
- polydipsia
- uraemia
Symptoms and signs (cont)

- “Bones”:
  - radiologic osteoporosis
  - osteomalacia or rickets
  - arthritis
  - osteitis fibrosa cystica with:
    - subperiostal resorption
    - osteoclastomas
    - bone cysts
    - “salt and pepper” skull
“Psychic moans”:
- lethargy, fatigue
- depression
- memory loss
- psychoses / paranoia
- personality change, neurosis
- confusion, stupor, coma

“Abdominal groans”:
- indigestion, nausea, vomiting
- constipation
- peptic ulcer
- pancreatitis
- proximal muscle weakness
- keratitis, conjunctivitis
- hypertension
- itching
- short QT interval, dysrhythmias
Causes of primary hyperparathyroidism

- Solitary adenoma: 80% of cases of hyperparathyroidism
  - seldom: multiple adenomas
- Hyperplasia: 12-15% of cases
  - usually as part of MEN syndromes
- Carcinoma: 1-2% of cases

Our patient (continue)

- Thoracotomy performed
- Large tumour removed, weight = 501g
Mass: 501g
Measurements: 130 x 125 x 75mm

Histology in keeping with:

- Brown tumour of hyperparathyroidism
  (osteitis fibrosa cystica)
Treatment of 1º hyperparathyroidism

- Severe hyperparathyroidism (Ca>3.7-4.5): surgery is mandatory as soon as diagnosis is confirmed
- Asymptomatic hyperparathyroidism: can probably manage it medically if patient age > 50 and no indications for surgery
Medical therapy

- Careful follow-up:
  - at time of initial evaluation: creatinine clearance, 24h u-Ca, abd X-r + U/S
  - Ca 2x/year
  - serum creatinine annually
  - bone density annually (lumbar spine, hip, forearm)

- Bisphosphonates eg alendronate
- Raloxifene (SERMS)
- Calcimimetics (still experimental)

Surgery indicated in primary hyperparathyroidism if:

- Serum Ca >0.25mmol/L above upper limits of normal
- Previous episode of life-threatening hyperCa
- Creatinine clearance < 60ml/min
- Kidney stone(s)
- BMD: T-score < -2.5 any site and / or past fragility fracture
- Patient < 50 years
- Long-term medical surveillance not desired / possible
**Surgery**

- Adenoma: usually already localized preop by parathyroid scan (99mTc sestamibi scan)
- Examine all 4 parathyroids intraoperatively; remove diseased one
- Minimally invasive approach
- If hyperplasia: remove 3 ½ glands, can implant ½ on forearm
- If malignant: be careful to remove with capsule intact

**Treatment of severe hypercalcaemia**

**Most useful therapies:**
- Hydration with saline
- Forced diuresis: saline + loop diuretic
- Bisphosphonates (IV)
- Calcitonin

**Special use therapies:**
- Glucocorticoids
- Dialysis
SECONDARY HYPERPARATHYROIDISM

Occurs in:
- End-stage renal failure (most often)
- Vitamin D deficiency
- Idiopathic hypercalciuria
- Long-term lithium therapy

→ Hypocalcaemia = common denominator in initiating 2° hyperparathyroidism

TERTIARY HYPERPARATHYROIDISM

- Occurs in chronic renal failure
- Long-standing hypoCa leads to hyperplasia of the parathyroids = 2° hyperparathyroidism (↑ PTH, ↓ Ca, ↑ phosphate)
- One or more previously hyperplastic parathyroid gland develops autonomous function (overactivity)
- Now: ↑ PTH, ↑ Ca, ↓/N phosphate
- Requires surgery
MEN

- Rare autosomal dominant condition
- Hyperplasia / adenomas / malignancies in multiple endocrine glands
- MEN 1 (3 P’s)
  - Primary hyperparathyroidism
  - Pituitary tumours
  - Endocrine pancreas tumours
- MEN 2A
  - Primary hyperparathyroidism
  - Medullary thyroid Ca
  - Phaeochromocytoma

HYPOCALCAEMIA
Case presentation

- 16 year old patient from Mamelodi
- Admitted to SBAH ICU with:
  - status epilepticus
  - aspiration pneumonia
- Already intubated
- Only history available: known epileptic x 1 year (on Epanutin)

Blood tests:
- Ca = 0.96 mmol/L (2.15-2.45)
- Ca(corr) = 1.18 mmol/L (2.15-2.45)
- Ionized Ca = 0.87 mmol/L (1.20-1.38)
- Phosphate = 2.09 mmol/L (0.80-1.40)
CAUSES OF HYPOCALCAEMIA

- **PTH absent:**
  - hereditary hypoparathyroidism
  - acquired hypoparathyroidism
  - hypomagnesaemia

- **PTH ineffective:**
  - chronic renal failure
  - active vitamin D lacking
    - ↓ dietary intake or sunlight
  - active vitamin D ineffective
    - malabsorption
  - pseudohypoparathyroidism
- **PTH overwhelmed:**
  - severe, acute hyperphosphataemia
    - acute renal failure
    - rhabdomyolysis
  - after parathyroidectomy in a patient with osteitis fibrosa

**Signs and symptoms**

- **Cardiac:**
  - prolonged QT interval
  - refractory congestive cardiac failure
Signs and symptoms (cont)

- **Ophthalmologic:**
  - subcapsular cataract

- **Dermatologic:**
  - skin dry, flaky; nails brittle
  - impetigo herpetiformis
  - pustular psoriasis

Signs and symptoms (cont)

- **Neuromuscular:**
  - Chvostek’s sign
Signs and symptoms (cont)

- Neuromuscular:
  - tetany, carpopedal spasm
  - Trousseau’s sign

Signs and symptoms (cont)

- Neuromuscular:
  - mental retardation in children
  - other: pseudotumour cerebri, papilloedema, confusion, lassitude, laringo/brochospasm
  - basal ganglia calcifications
Our patient’s results

- Mg = 0.51 mmol/L (0.65-1.10)
- 25-OH-Vitamin D = 51 nmol/L (49.92-174.72)
- PTH = <1.0 ng/L (12 – 88)

- **NB:** Correct magnesium deficiency first!
- PTH remained low
- Epileptiforme changes on EEG
- Brain calcifications
Final diagnosis

= Primary hypoparathyroidism

HYPOPARATHYROIDISM

Acquired:

- Surgery
- Infiltration
- Radiation-induced
- Infection
- Transient hypoparathyroidism post surgery for hyperparathyroidism
**Hereditary:**

- idiopathic/hereditary hypoparathyroidism
- polyglandular autoimmune type 1 deficiency

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**Autoimmune Poly-endocrine syndromes**

**Type 1**
- Addison's (60%)
- Hypoparathyroidism (89%)
- T1DM (4%)
- Primary hypothyroidism (12%)
- Gonadal failure (45%)
- Mucocutaneous candidiasis (75%)
- Manifest early in life, usually before 15 yr

**Type 2**
- Addison's (100%)
- Autoimmune thyroid disease (70%)
- T1DM (50%)
- Gonadal failure (5 – 50%)
- Vitiligo
- Pernicious anaemia
- Manifest between 20 and 30 yr
PSEUDOHYPOPARATHYROIDISM (PHP)

- Hereditary disorder, characterized by symptoms and signs of hypoparathyroidism, typically in association with distinctive skeletal and developmental defects
- Deficient end-organ response to PTH (resistance)
- ↓ Ca, ↑ phosphate, ↑ PTH

Type Ia (Albright’s hereditary osteodystrophy = AHO)
- short stature
- round face
- skeletal anomalies (brachydactyly; short 4th, 5th metacarpals, metatarsals)
- heterotopic calcifications (also basal ganglia)
  + other endocrinopathies esp hypothyroidism
PSEUDOPSEUDOHYPO-PARATHYROIDISM (PPHP)

- Normal Ca, phosphate, PTH
- But: clinically Albright’s hereditary osteodystrophy
- Occurs sometimes in families with PHP (somatic phenotype, without Ca disturbances)
- No treatment necessary
TREATMENT OF HYPOPARATHYROIDISM

- **Active vitamin D**: 1,25(OH)2D3 = calcitriol (Rocaltrol): 0.5-1μg/d; can also use One-Alpha
- Combined with high oral Ca intake (>=1g/d)
- If not available: normal Vitamin D 40,000-120,000U/d
- Be careful: can develop kidney stones
- Thiazides can ↑ s-Ca, ↓ u-Ca, ↓ kidney stones
  - helpful in brittle hypoparathyroidism
PAGET’S DISEASE

- Disorder of bone remodelling
- Excessive resorption with compensatory increase in bone formation
- New bone is structurally abnormal and therefore weak
- Increase in local blood flow
- Increase in fibrous tissue in adjacent marrow

Paget’s (cont)

- Older patients > 60 years
- Often incidentally detected on X-rays
- Diagnosis:
  - high ALP
  - Ca often increases when immobilized
  - X-ray findings
Clinical picture

- Bone pain: often of pelvis or spine
- Joint pain: if the area involved is close to a joint or causes deformity, it can lead to cartilage damage or osteoarthritis

Deformities: tibia or skull
Complications

- Increased blood flow: heart failure
- Nerve compression:
  - VIII: deafness; also II, V, VII
- Bone weakness:
  - pathological fractures
- Rarely osteogenic sarcoma
- Deformities
- Osteoarthritis

Treatment

- Asymptomatic: nil
- Osteoarthritis: symptomatically
- Bisphosphonates
- Surgery for deformities