An Approach to a Child with Hypercalcaemia

Raja Padidela
Consultant in Paediatric Endocrinology
Royal Manchester Children's Hospital
OUTLINE

- Regulation of serum Calcium concentration
- Disorders causing chronic hypercalcaemia
- Treatment
- Case history
Regulation of serum Calcium Concentration
Serum concentration of total Calcium, adjusted for albumin usually provided by biochemistry laboratories

Bound Calcium + Ionised Calcium = 2.2-2.7 (1.1-1.3)

Serum Calcium Concentration

Albumin Protein Phosphate Citrate

$\text{Ca}^{2+}$
Regulation of Serum Calcium Concentration by Parathyroid Hormone (PTH) & 1,25(OH)$_2$D3

From AJCN. 2004; 80,(6) 1689-96.
The Extracellular Ca\textsuperscript{2+} Sensing Receptor (CaSR)

Hypocalcaemia Caused by Mutations or Antibodies to CaSR
Schematic representation of the sigmoidal relationship between ionized Ca (Ca\(^{2+}\)) and intact PTH secretion

J Clin Endocrinol Metab 1989; 69:593–9
Hypercalcaemia
Symptoms of Hypercalcaemia

- **Gastrointestinal symptoms.** Nausea, anorexia, vomiting & weight loss


- **CNS & Musculoskeletal symptoms.** Lethargy & muscle weakness. Older children may present with psychiatric symptoms.

- **Cardiac effects.** Hypertension. Short QT interval
Approach to hypercalcaemia

- PTH dependent/independent
- Abnormality in PTH secretion
  - Hyposecretion of PTH - Hypocalcaemia
  - Hypersecretion of PTH - hypercalcaemia
High PTH

• Primary hyperparathyroidism
• Familial isolated primary hyperparathyroidism
• MEN 1, 2 & 4
• Neonatal severe hyperparathyroidism - AR mutation of inactivating Ca\(^{2+}\) sensing receptor

Normal PTH

Familial hypocalciuric hypercalcaemia - AD mutation of Ca\(^{2+}\) sensing receptor

Low PTH

• Williams syndrome
• Idiopathic hypercalcaemia of infancy
• Vitamin D toxicity
• Increased 1,25(OH)D\(_2\) synthesis
• Subcutaneous fat necrosis
• Sarcoidosis & Tuberculosis

Measure PTH

Increased urinary Ca\(^{2+}\)

Decreased urinary Ca\(^{2+}\)

Increased Ca\(^{2+}\) Absorption

Increased 1,25(OH)D\(_2\) Synthesis
Treatment of Hypercalcaemia

- Hydration
- Low Ca & Vitamin D free diet
- Corticosteroids
- Bisphosphonates
- Specific Rx e.g. parathyrodeectomy

Monitoring

- Urine Ca/Cr (<0.56)
- Renal Ultrasound Scan
Case history
Case history

● Failure to thrive in a 8 mo old female infant
● Term delivery, Bwt 2.6 kg, nonconsanguineous parents
● Exclusively breast fed till 3 mo of age
● Poor weight gain was noted and hence commenced on formula feeds & healthy start vitamin supplementation (300 IU/day)
History at presentation - 8 months

- Poor weight gain
- Reasonable good feeding
- History of developmental delay, mainly gross motor with hypotonia ("my baby is like a rag doll")
- History of irritability
- Frequent nappy changes which were heavy
Clinical findings

- At 10 mo
- Wt- 6.2kg (<0.4\textsuperscript{th} cent; -3.7SDS)
- Length- 65.4 cm (0.4\textsuperscript{th}-2\textsuperscript{nd} cent; -2.2)
- Head circumference- 42cm (<0.4\textsuperscript{th} cent)
Results

- Coeliac screen - normal
- CRP and inflammatory markers - normal
- FBC - Hb 9.9 (10.5-13.5), rest normal
- CCa-3.92, AlkPhos-132(180-400), PO4-1.70 (1.36-2.26), Mg-0.92 (0.70-1.0)
Results

- Coeliac screen - normal
- CRP and inflammatory markers - normal
- FBC- Hb 9.9 (10.5-13.5), rest normal
- CCa-3.92, AlkPhos-132(180-400), PO4-1.70 (1.36-2.26), Mg-0.92 (0.70-1.0)
- What other investigations would you consider?
Results

- PTH 0.6 pmol/l (1.6-6.8)
- Vitamin D 92 nmol/L (50-150)
- Urinary Ca/Crt ratio  2.5 (<0.56)
- What is your interpretation of these results?
- Primary hyperparathyroidism
- Familial isolated primary hyperparathyroidism
  - MEN 1, 2 & 4
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- Increased urinary Ca\(^{2+}\)
- Increased Ca\(^{2+}\) Absorption
- Increased 1,25(OH)D\(_2\) Synthesis
Management

- Commenced on low calcium diet- locasol milk (Ca-7mg/100ml)
- Breast feeds contain 30-40mg/100ml, formula feeds contain 50-60mg/100ml of calcium and cow’s milk contains 100-120mg/100ml.
- Hydration- Normal saline 150ml/kg/day.
Clinical and biochemical progress

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<th>Na (133-146)</th>
<th>K (3.5-5.5)</th>
<th>Ur (2.5-7.8)</th>
<th>Cr (15-37)</th>
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- Improvement in tone
- Feeding improved
- Gradual decrease in polyuria and polydipsia
- Continues on low calcium containing diet

Low Ca diet

PTH - 0.6 pmol/L (1.6-6.8)
Vitamin D - 92nmol/L (50-150 nmol/L)
Definitive diagnosis

**Williams Syndrome**

- Important information from clinical findings
- Mild dysmorphic features -
  - Depressed nasal bridge
  - Bulbous nose
  - Long philtrum, thick lips, and epicanthal folds
- Hemizygous submicroscopic deletions of 7q11.23
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<td>WS-bHLH</td>
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*Tentative nomenclature. No official gene symbol or gene name has been approved.*
Management of Absorptive Hypercalcaemia

- Dietary Ca restriction
- Avoid vitamin D supplements
- Use Sun Block creams
- Avoid ‘Hard water’
- Short-term Rx with Oral Corticosteroids (Prednisolone 2mg/kg daily)

- < 7 mg Ca per 100 ml
  (usual formulae ~ 50 to 90 mg per 100 ml)
- No Vitamin D !!
- FTND at 36 weeks gest weighing 2.7 kgs
- Admitted on Day 6: poor feeding & hypotonia
- Ca 5.5 mmol/l & 6.03 mmol/l
- Phosphate 1.18 mmol/l & ALP 457 iu/l
- Serum PTH 650 & 950 pmols/l (10 - 80)
- Craniotabes & skeletal demineralisation
Neonatal Severe Primary Hyperparathyroidism

Distant Cousins

Ca 2.6
PTH 39 (10-60)
U Ca/Cr 0.24

Ca 2.65
PTH 42 (10-60)
U Ca/Cr 0.13

Ca 6.03
PTH 950 (10-60)
U Ca/Cr 0.07
No Nephrocalcinosis
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Neonatal Severe Primary Hyperparathyroidism

- SURGERY at ~ 6 weeks
- Excision of two enlarged parathyroid glands on the inferior pole
- No parathyroid tissue in the thymus
- Clear cell hyperplasia
- I.V. calcium gluconate & oral Alfacalcidol
- 48 hours after surgery PTH 34 pmol/l (10-60)
- 99m-Tc MIBI scan – no parathyroid tissue seen
Neonatal Severe Primary Hyperparathyroidism

- A C to T point mutation in exon 4 of the CaSr receptor gene.
- Results in truncated extracellular domain of the CaSr receptor.
- Aysha homozygous & parents heterozygous.
Thank You