Hypercalcemia: When to Worry, When to Treat!

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Michael A. Levine has no financial relationships to disclose or Conflicts of Interest to resolve.

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Mineral Metabolism: A Short Course

Hypercalcemia

- Hypercalcemia is rare in children
  - Frequently iatrogenic
  - Often discovered on routine chemistry panel
- Hypercalcemia may be “factitious”
  - Dehydration can increase total calcium level
  - Normal range for infants different than adults
Serum albumin and pH can influence serum calcium concentration

- 50% of total serum calcium is protein bound
- Albumin is primary binding protein
- Changes in albumin level affect calcium concentration
- pH affects [Ca$^{++}$]

Age-related Normal Values for Total Serum Calcium Concentration

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Infant</th>
<th>0-0.25</th>
<th>8.8-11.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-5</td>
<td>9.4-10.8</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>6-12</td>
<td>9.4-10.3</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>20</td>
<td>9.1-10.2</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>20</td>
<td>8.8-10.0</td>
<td></td>
</tr>
</tbody>
</table>

After Portale, AA 1999 Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 4th Ed.

Age-related Normal Values for Urinary Calcium/Creatinine Ratio

<table>
<thead>
<tr>
<th>Age</th>
<th>UCa/Cr 95th percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td></td>
</tr>
<tr>
<td>&lt; 7 months</td>
<td>0.86 mg/mg</td>
</tr>
<tr>
<td>7 to 18 months</td>
<td>0.60 mg/mg</td>
</tr>
<tr>
<td>Children</td>
<td></td>
</tr>
<tr>
<td>19 m to 6 yrs</td>
<td>0.42 mg/mg</td>
</tr>
<tr>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.22 mg/mg</td>
</tr>
</tbody>
</table>


Clinical Severity of Hypercalcemia

- Ranges from asymptomatic laboratory finding to life-threatening illness
  - Lethargy, irritability, polyuria, constipation, dehydration, vomiting, failure to thrive
- Depends upon both the degree and duration of hypercalcemia
  - Nephrocalcinosis, hypertension, band keratopathy
- Reflects the level of ionized calcium
- Children are more adaptive than adults
What Causes Hypercalcemia?

- Which is the most important mechanism for hypercalcemia?
  
  A. Increased absorption of calcium from gastrointestinal tract?
  B. Increased resorption of calcium from skeleton?
  C. Decreased renal excretion of calcium?

Pathophysiology of FHH and NSHPT

- Enhanced reabsorption of calcium in renal proximal tubule even in absence of PTH.
- Increased PTH secretion despite hypercalcemia.
- Serum magnesium slightly elevated.
- Inactivating mutations in the CASR gene encoding the calcium-sensing receptor in most patients.
  - Heterozygous mutations generally cause FHH
  - Homozygous mutations generally cause NSHPT

Diagnosis of Hypercalcemia by Typical Age of Onset

- Birth
- 10 y
- 20 y
- 40 y
- 60 y
- 80 y

FHH
SQ fat necrosis/lactase deficiency
Williams/Idiopathic Hypercalcemia
MEN1 – MEN2a
Familial Hyperparathyroidism
Parathyroid adenoma
Neoplasia

Neonatal Severe Hyperparathyroidism (NSHPT)

- Life-threatening hypercalcemia within first few days of life.
- Very low urinary calcium excretion and (FeCa) is typically less than 0.01.
- PTH and serum 1,25(OH)\textsubscript{2}D are markedly elevated.
- Severe bone demineralization, fractures and growth plate defects.
- Failure to thrive and respiratory distress.
**Excessive Secretion of PTH Due to Inactivating Mutations of the CaSR**

- PTH gene
- mRNA
- PTH(1-84)
- Gq
- PLC
- Ca++
- ↑

**Medical Therapy for NSHPT**

- Saline not very effective.
- Calcitonin acts quickly, but produces only a modest reduction in serum calcium and tachyphylaxis occurs after several days.
- Intravenous bisphosphonates can normalize calcium within 72 hours.
- Cinacalcet as calcimimetic inhibits PTH secretion
  - Has been used successfully with and without bisphosphonates to treat infants with NSHPT.¹ ²


**Medical Therapy of FHH**

- Generally benign and asymptomatic, so no specific therapy indicated.
- SOME cases may be symptomatic and might benefit from a trial of cinacalcet

**Hypercalcemia Associated with Vitamin D Sensitivity**

- Subcutaneous fat necrosis
- Williams syndrome
- Idiopathic hypercalcemia
Subcutaneous Fat Necrosis

- Occurs in newborns several days to weeks after traumatic birth
- Indurated, violet subcutaneous nodules
  - On face, trunk, buttocks, and proximal extremities
  - Histology shows mononuclear and giant cells
- Hypercalcemia and/or hypercalciuria occur within several weeks and may be protracted
- Increased serum calcitriol and decreased PTH

Williams Syndrome

- ELN gene deletion 7q11 by FISH or microarray
- Calcium problems
  - Onset at 3-4 months, resolves by age 4 years
  - Hypercalcemia (15%)
  - Hypercalciuria (30%)
  - Nephrocalcinosis and nephrolithiasis rare
  - Sensitivity to Vitamin D, but PTH and 1,25(OH)₂D are generally normal.

Idiopathic Hypercalcemia

- No features of Williams syndrome
- Increased skeletal resorption
- Increased gut absorption of calcium
- Elevated levels of 1,25(OH)₂D
- PTH is low or suppressed
- Biallelic inactivation of CYP24A can be basis


Treatment of Hypercalcemia

Which of the following agents would you avoid when treating a child with hypercalcemia?

A. Intravenous saline
B. Cape Cod Potato Chips
C. Utz Potato Chips
D. Furosemide
Medical Therapy

- Treat if hypercalcemia is symptomatic or nephrocalcinosis is present.
  - Diuresis with i.v. saline or dietary salt
  - Calcitonin may be useful short term.
  - Reduce vitamin D and calcium intake
  - Calcilo-XD infant formula or breastmilk
- Monitor urinary calcium excretion and renal calcification.
- Loop diuretics may drop GFR and worsen hypercalcemia!

Laboratory Features of Primary Hyperparathyroidism

- Blood
  - Elevated total and/or ionized calcium
  - Phosphate low, chloride may be elevated
  - Elevated levels of intact PTH and calcitriol
- Urine
  - Decreased tubular reabsorption of phosphate
  - Normal or elevated calcium (FeCa > 0.01)

Rule out FHH!!!

Utility of PTH Measurement

- 7 to 18% of iPTH values may be in normal range in patients with surgically proven PHPT.\(^1\)^\(^2\)

Screening for Bone Loss in Primary Hyperparathyroidism

1/3 Site of radius
Cortical rich site

Lumbar Spine
Cortical 34%, Trabecular 66%

Trochanter
Cortical 50%, Trabecular 50%

Femoral Neck
Cortical 75%, Trabecular 25%

Primary Hyperparathyroidism: 2008 International Workshop Indications for Surgery

- Serum calcium 11.5 mg/dL or > 1 mg/dL above normal.
- Reduced BMD with T <-2.5 at any site or prior fragility fracture (Z score < age 50 yrs).
- Renal stones (urine calcium > 400 mg/d).
- Creatinine clearance reduced to < 60 ml/min.
- Age younger than 50 years.
- Patient cannot be monitored reliably.

Localization of Parathyroid Adenoma

What is best method to localize a parathyroid adenoma?

A. Sestimibi scan
B. Neck ultrasound
C. MRI
D. CT
E. Refer to an experienced surgeon

Guidelines for Surgical Management of PHPT

- Refer to a center with experienced parathyroid surgeon.
- Intra-operative monitoring of PTH levels improve outcomes and reduce surgical time.
- Pre-operative localization of parathyroid adenoma facilitates minimally invasive parathyroid surgery (MIPS).
Medical Therapy for PHPT

- Intravenous hydration with normal saline.
- Maintain normal vitamin D and calcium intake.
- Calcitonin acts quickly, but produces only modest reduction in serum calcium and tachyphylaxis occurs after several days.
- Intravenous bisphosphonates can normalize calcium within 72 hours.
- Cinacalcet can inhibit PTH secretion

Hypercalcemia of Malignancy: Clinical Presentation

- Complicates 1% of cancer
  - Acute leukemia, rhabdomyosarcoma, lymphoma, ovary and liver
- Acute and symptomatic
- Can be associated with bone demineralization and fractures
- Malignancy usually obvious

Other Causes of Hypercalcemia in Infants and Children

- Renal tubular acidosis
- Ketogenic diet
- Adrenal insufficiency
- Hyperthyroidism
- Immobilization
- Chronic inflammatory disorders

Management of Hypercalcemia

- Maintain adequate fluids and avoid dehydration
- Urgent therapy may require intravenous saline, calcitonin and bisphosphonates
- Chronic management may require long-term calcitonin or intermittent intravenous bisphosphonates
- Chronic medical therapy is not well established for most forms of non-parathyroid hypercalcemia
The end.