ENDORAMER

HOW SHOULD WE TREAT FHH? IS THIS FHH?

DISHA KUMAR NARANG, M.D.
NOVEMBER 6, 2014
OUR PATIENT

• 11-years, 9 months male presents to clinic with weakness and fatigue over the last 4 weeks
  • “My arms feel like dead weights”
  • Occasional paresthesias in arms and legs
  • No numbness or perioral tingling
  • Occasional epigastric and lower abdominal pain
PHYSICAL EXAM

• Vitals: T 35.6; HR 89; BP 101/65; RR 20; Weight: 42.4kg; Height: 151.9cm
  • 50th percentile for height and weight
• Gen: Well-developed; NAD
• HEENT: Atraumatic; PERRLA; MMM; normal dentition; clear oropharynx; neck supple; no adenopathy; no thyromegaly
• CV: RRR; normal S1/S2; no murmur/gallop/rub
• Pulm: Normal effort; expiratory wheezes bilaterally
• Abd: Soft, non-tender, non-distended
• GU: Tanner II axillary hair growth; Tanner IV pubic hair growth; testes 3cm bilaterally
• MSK: Normal ROM; no deformities
• Neuro: AAOx3; normal reflexes
• Skin: Warm; no rash; acne on forehead
PATIENT HISTORY

• PMH
  • Familial hypocalciuric hypercalcemia
  • Hypospadias
  • Nonallergic rhinitis
  • Asthma
  • Psychological trauma (murder witness)

• PSH
  • Hypospadias repairs

• Family History
  • Pt is adopted – Family history unknown

• Medications
  • Albuterol
  • Fluticasone
  • Loratidine
  • Prednisone
  • Tretinoin gel

• Allergies
  • Cats

• Social History
  • Lives with mother, aunt, and uncle
  • Currently in 6th grade
  • No tobacco/EtOH/illicits
DETAILED PATIENT HISTORY

- Born at 37 weeks, after pregnancy complicated by no prenatal care
- Born at home, and developed respiratory distress at home → transferred to Cook County Hospital, where he was intubated and had significant complications (admitted in NICU for 6 weeks)
  - Mother had history of psychiatric disorder and cognitive impairment
  - Patient was placed in foster care at 6 weeks of age
- Developed chronic constipation
- Admitted to UCMC at age 4 months after **Ca 13.1 mg/dL** incidentally found on labs
INITIAL HYPERCALCEMIA WORK-UP (2003)

- **Outpatient Follow-up:**
  - Ca 12.7**
  - Mg 2.4
  - Phos 4.8
  - 1,25-dihydroxy-Vit D 55
  - 25-OH-Vit D 44
  - Parathyroid ultrasound: No evidence of adenoma

- Ionized Ca: 7.6 mg/dL
- PTH: 27
- Vit D: Not collected
- Random Ca/Cr clearance ratio: 5
- TSH: 2.6
INITIAL HYPERCALCEMIA WORK-UP (2003)

- Patient had several dysmorphic features and abnormal neurological exam, with mild to moderate delays
  - Chromosome and FISH testing for Williams Syndrome – Negative
  - Skeletal survey – Abnormalities of proximal femurs with irregular metastases and diatheses; normal bone mineralization; no other bony abnormalities
INITIAL ASSESSMENT

- Hypercalcemia of unknown etiology
  - Ruled out: Williams Syndrome, Jansen Syndrome, FHH, subcutaneous fat necrosis, malignancy, thyroid disease, congenital lactase deficiency
  - Presumptive diagnoses:
    - Mild hyperparathyroidism
    - Idiopathic infantile hypercalcemia

- Treatment plan:
  - Continue observation as patient is asymptomatic and development progressing appropriately
DO WE HAVE A DIAGNOSIS?

• 2004: 8-hour timed urine collection:
  • Calcium creatinine clearance ratio: 0.0085
    • Ca Cr clearance ratio > 0.01 → Primary hyperparathyroidism
    • Ca Cr clearance ratio < 0.01 → FHH or primary hyperparathyroidism with Vitamin D deficiency
  • Familial hypocalciuric hypercalcemia
    • Treatment Plan? → Observe
UPON RETURN TO FOLLOW-UP IN 2010

<table>
<thead>
<tr>
<th></th>
<th>140</th>
<th>106</th>
<th>13</th>
<th>Ca 12.0</th>
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<tr>
<td></td>
<td>3.9</td>
<td>27</td>
<td>0.5</td>
<td>100</td>
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</tbody>
</table>

PTH – 46

Urinalysis:
- Color – Pale yellow
- Clarity – Clear
- Spec Grav – 1.023
- pH – 5.5
- Leuk Est – Neg
- Nitrite – Neg
- Protein – Neg
- Blood – Neg
- Gluc – Neg
- Ketones – Neg
- UBG – 0.2

Bladder and Kidney U/S: Normal

<table>
<thead>
<tr>
<th></th>
<th>7.3</th>
<th>4.6</th>
<th>0.2</th>
<th>26</th>
<th>20</th>
<th>317</th>
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### CURRENT LABS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Creatinine</td>
<td>140</td>
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<tr>
<td>Urea nitrogen</td>
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<tr>
<td>BUN</td>
<td>10</td>
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<tr>
<td>Sodium</td>
<td>85</td>
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<tr>
<td>Potassium</td>
<td>3.9</td>
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<tr>
<td>Chloride</td>
<td>23</td>
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<tr>
<td>Carbon dioxide</td>
<td>0.6</td>
</tr>
<tr>
<td>Calcium</td>
<td>12.4</td>
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<tr>
<td>Magnesium</td>
<td>2.4</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>3.1</td>
</tr>
<tr>
<td>Urinalysis:</td>
<td></td>
</tr>
<tr>
<td>Color</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>Clarity</td>
<td>Slightly turbid</td>
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<tr>
<td>Specific gravity</td>
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<tr>
<td>pH</td>
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<tr>
<td>Leukocyte esterase</td>
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<tr>
<td>Nitrite</td>
<td>Neg</td>
</tr>
<tr>
<td>Protein</td>
<td>Neg</td>
</tr>
<tr>
<td>Blood</td>
<td>Neg</td>
</tr>
<tr>
<td>Glucose</td>
<td>Neg</td>
</tr>
<tr>
<td>Ketones</td>
<td>Neg</td>
</tr>
<tr>
<td>UBG</td>
<td>0.2</td>
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<tr>
<td>Red blood cells</td>
<td>None</td>
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<tr>
<td>White blood cells</td>
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<tr>
<td>Random urine calcium</td>
<td>7.1</td>
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<tr>
<td>Parathyroid hormone</td>
<td>75</td>
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<tr>
<td>25-OH-Vitamin D</td>
<td>23</td>
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<tr>
<td>Thyroid-stimulating hormone</td>
<td>2.44</td>
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CALCIUM TREND
PTH TREND

Graph Legend
- PTH, Intact (High)
- PTH, Intact
- PTH, Intact (Low)
CLINICAL QUESTIONS

1. DO WE THINK THIS IS FHH?

2. SINCE THE PATIENT IS SYMPTOMATIC, WHAT WOULD TREATMENT BE?

3. WHAT IS THE ROLE OF CALCIMIMETICS IN THE TREATMENT OF FHH?
1. Hypercalcemia
2. Reduced renal Ca excretion
3. Family history compatible with autosomal dominant heritability
4. Normal plasma PTH
   - 24% of patients have elevated plasma PTH
5. Recurrent hypercalcemia after parathyroidectomy
6. Symptomatic or oligosymptomatic disease
7. Significant mutation in the CaSR gene, or verified familial occurrence of hypocaliuria
FHH – DIAGNOSTIC CRITERIA¹

1. Hypercalcemia **
2. Reduced renal Ca excretion
3. Family history compatible with autosomal dominant heritability
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5. Recurrent hypercalcemia after parathyroidectomy
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Normoparathyroid or hyperparathyroid hypercalcemic patients
Asymptomatic or oligosymptomatic disease

- CCCR
- CCCR

CCCRI < 0.020
CCCRI ≥ 0.020

- CASR
- CASR

CCCRI < 0.020
CCCRI < 0.020
CCCRI < 0.020
CASR positive
CASR negative

- PHPT

- FHH
FHH - PHYSIOLOGY

- Autosomal dominant inheritance with high penetrance
- Approximately 200 mutations of CaSR have been identified
- Affected heterozygous patients present in childhood
- FHH-like syndromes can be caused by CaSR Ab’s that modulate the shape of the CaSR molecule imitating a CaSR mutation
FHH - PHYSIOLOGY

- Caused by inactivating mutations in the gene for the calcium-sensing receptor (CaSR)
- Main function: Regulate calcium balance
- CaSR expressed in multiple tissues
  - Parathyroid glands, kidneys, bone marrow, osteoblasts/osteoclasts, thyroid C-cells, intestine

Elevated Ca levels

- Stimulation of CaSR
- Inhibition of PTH secretion
- Tonic suppression of parathyroid cellular proliferation
In the kidneys, CaSR is expressed throughout most of the nephron.

- Elevated Ca levels
  - Stimulation of CaSR
  - Reduced urinary concentration capacity from reduction of Aquaporin-2
  - Increased renal Ca excretion and increased tubular reabsorption of Ca
WHY IS FHH DIAGNOSIS QUESTIONED?

- Serum Ca is usually below 12 mg/dL (8)
  - Highest reported serum Ca in FHH is 14.5 mg/dL
- Serum phosphorus is lower in patients with FHH than normal, but not so low as the mean value in primary hyperparathyroidism
- Serum Mg is usually in the upper limit of normal in FHH, and lower limit of normal in hyperparathyroidism
- While 24-hour Ca excretion in patients with FHH is lower than in primary hyperparathyroidism, there is overlap between the 2 disorders
- PTH values are within the normal range in patients with FHH, but can be in the upper limit of normal in primary hyperparathyroidism
WHAT ELSE COULD THIS BE?

• Primary hyperparathyroidism (PHPT)\(^9\)
  • Greater morbidity in children and adolescents; 5% of all cases of PHPT
  • High prevalence of heterozygous CaSR mutations
  • Single or multiple parathyroid adenomas
  • Typical manifestations:
    • Hypercalcemia
    • Hypophosphatemia
    • Hypercalciuria (can be low when there is co-existing Vitamin D deficiency)
    • Elevated or inappropriately normal PTH
  • Treatment
    • Mild hypercalcemia → calcimimetic
    • Parathyroidectomy
WHAT ELSE COULD THIS BE?

- Mutations in the CaSR (biallelic) are also associated with neonatal severe hyperparathyroidism (NSPHT) (7,8)
  - Primary hyperparathyroidism associated with very high levels of serum Ca and PTH, and hypocalciuria
  - Infants have hypophosphatemia and osteopenia at birth
  - Children symptomatic within first week of life
  - Treatment: urgent subtotal parathyroidectomy
    - Bisphosphonates and calcimimetics have been used in some cases to quickly reduce calcium levels
FHH - PROGNOSIS

• Good prognosis with normal life expectancy
• Clinical consequences
  • Rare cases of chondrocalcinosis and acute pancreatitis
  • Avoid unnecessary parathyroidectomy
PROPOSED TREATMENTS

• Calcimimetics (cinacalcet/Sensipar) – Allosteric modulators of the CaSR
  • Increases sensitivity and expression of the CaSR → Enhances CaSR signal transduction → Shifts concentration-response curve to the left → Less suppression of PTH release from parathyroid glands at distinct serum Ca levels
MECHANISM

• Mechanism by which calcimimetics are capable of restoring sensitivity to serum calcium, in spite of the mutation in CaSR, is still under investigation
  • In human CaSR, both intra- and extracellular mutating receptors respond (4)
  • Deactivation mutations cause a decrease in the sensitivity of the CaSR to calcium, which is restored back with the addition of a calcimimetic agent (5)
Beneficial effect of cinacalcet in a child with familial hypocalciuric hypercalcemia

Uri S. Alon · René G. VanDeVoorde

- 6-year-old child with FHH (and positive family history) in whom hypercalcemia was thought to interfere with surgical scar healing

- Treated with cinacalcet for 12 months
  - Started with 30mg qday, and after 1 week doubled to 30mg BID
  - Serum Ca and PTH decreased to normal ranges (dose response)

- F/U visit with ENT:
  - Well-healed tissue with no calcifications; improved hearing
BACK TO OUR PATIENT

• Given the uptrend in our patient’s PTH over the last 10 years, he likely needs re-evaluation
  • FHH?
  • Primary hyperparathyroidism?
  • Decreased parathyroid gland sensitivity causing increasing PTH?

• What should our next steps be?
  • 24-hour urine calcium/creatinine clearance ratio
  • Genetic testing
  • Imaging of parathyroids
REPEAT LABS
(2 WEEKS LATER)

Ca 12.1
Mg 2.4
Phos 2.8
Ionized Ca – 6.27
TREATMENT

- **Standard approach to hypercalcemia**
  - **Mild-moderate hypercalcemia (<12-14 mg/dL)**
    - Immediate treatment not required
    - Adequate hydration
  - **Severe hypercalcemia (>14 mg/dL)**
    - Volume expansion (NS at 200-300 mL/hour)
    - Calcitonin (typically for symptomatic patients with Ca >14 mg/dL)
    - Zolendronic acid, pamidronate, denosumab
    - +/- Cinacalcet (depending on etiology of hypercalcemia)
    - +/- Furosemide
    - Parathyroidectomy in the case of PHPT
CONCLUSIONS

- Patients with FHH are typically asymptomatic and overall have a good prognosis.
- For patients with FHH who are symptomatic, consider conservative management with hydration first.
- Cinacalcet has been used in treatment of FHH, with dose response of Ca, Phos, and PTH levels.
- In this patient, concern that he may have primary hyperparathyroidism vs decreased parathyroid sensitivity causing increasing levels of PTH since infancy.
  - He will undergo 24-hour urine calcium and creatinine measurements, parathyroid imaging, and genetic testing.
REFERENCES


