Pseudohypoparathyroidism:
Case Presentation and Literature Review

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Disclosures

- Nothing to disclose
- Parental permission granted for use of photo

Objectives

- 1) Identify signs and symptoms of pseudo-hypoparathyroidism
- 2) Identify methods of properly diagnosing pseudohypoparathyroidism
- 3) Explain the underlying genetics of pseudo-hypoparathyroidism

Case Study

Birth History:

- Female infant born full-term, appropriate for gestational age, product of NSVD
- 1st NBMS→ Total T4: 4.2ug/dL (>6) and TSH <20mU/L
- 2nd NBMS→ Total T4: 5.1, TSH: 27
- Confirmatory serum testing at dol 11 revealed an elevated TSH: 35uIU/mL
- Started on levothyroxine: 25mcg qd

Early Hospitalizations

- 1mo: Fever of unknown source
  - TSH still elevated and increase levothyroxine to 37.5mcg
- 4mo: Failure to thrive
  - Started on elemental formula; maximize calories
- 5mo: Persistent failure to thrive and poor feeding

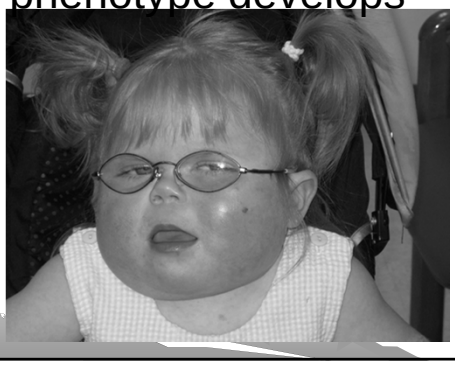
6mo: prolonged hospitalization

- Presented with multiple episodes of acute life threatening events (ALTE) and apnea
- Bronchoscopy→laryngospasm
- Swallow study→aspiration and hiatal hernia
- Pre-op eval for fundoplication, G-tube, and hiatal hernia repair included low serum Ca: 7.3mg/dL (LLN: 8.9)
- Consulted for further evaluation/management

Let's meet the patient

- Physical exam:
  - Round face
  - Slightly short nose
  - No shortening of 4^{th}/5^{th} metacarpals
  - No SQ calcifications
- Overall: not overly dramatic phenotype at that age (6mo)

But, by age 2yo: clear phenotype develops



Now back to the 6mo eval…

- Ionized Ca: 0.89mmol/L (LLN: 1.15)
- Phos: 6.1mg/dL (ULN: 5.7)
- Intact PTH: 953pg/ml (10-65)
- 25-OH vit D: 25ng/ml (10-55)
- 1,25-OH vit D: 74pg/ml (15-90)
- U Ca/Cr: <0.20

Diagnoses

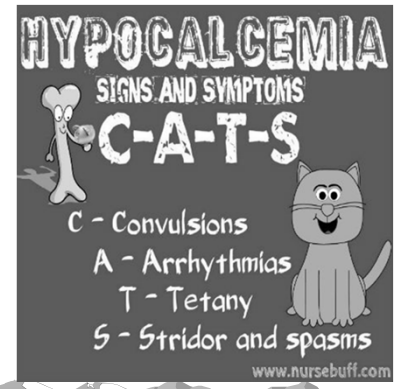
- Pseudohypoparathyroidism
  - Low Ca, high Phos, with super-high PTH
- Laryngospasm/ALTE
  - Secondary to hypocalcemia
- Hiatal hernia with aspiration

Objective 1:

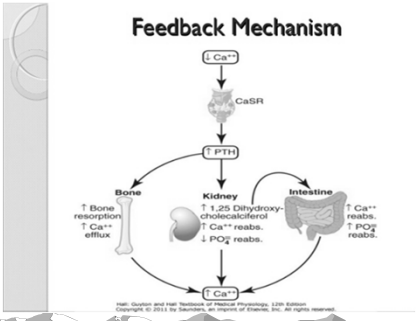
Signs and symptoms of pseudohypoparathyroidism

Hypocalcemia

- Irritability, jitteriness, seizures
- Laryngospasm, apnea, cyanosis
- Poor feeding/failure to thrive
- Muscle spasms, tetany
- EKG: long QT interval



Calcium Homeostasis-1



Calcium Homeostasis-2

- Hypoparathyroidism:
  - Low PTH→ low Ca and high Phos
- Hyperparathyroidism:
  - High PTH→ high Ca and low Phos
- Pseudo-hypoparathyroidism:
  - Looks like hypoparathyroidism: low Ca and high Phos
  - But, elevated PTH (due to resistance)

Albright's Hereditary Osteodystrophy (AHO) Phenotype

- Short stature
  - Decreased growth velocity
  - Early epiphyseal closure
- Developmental delays
- Round facies
- Obesity
- Short 3rd-5th metacarpals
- Subcutaneous calcifications

History of Pseudohypoparathyroidism

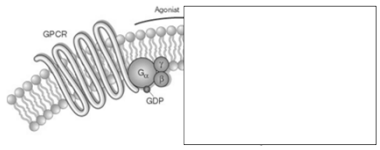
- The 1st hormone resistance syndrome identified (Albright, 1942)
  - 28yo woman with hypoCa seizures, MR, short/stocky, round face, short metacarpals/metatarsals, and SQ calcification
  - Rx: IM bovine PTH→no improvement in serum calcium
  - Surgical exploration of parathyroid glands→nl

Objective 2:

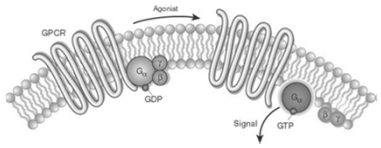
Diagnosing pseudohypoparathyroidism

Pathophysiology

- Loss of function in GNAS gene
  - G alpha subunit of the G-protein seven transmembrane receptor family



G-protein Cycle



- Inactive: alpha-GDP
- With receptor activation: GDP→GTP
  - Active alpha subunit dissociates
  - Stimulates adenylate cyclase→cAMP
  - Downstream activation

G Protein Receptor Defect: Leads to Resistance

- PTH
- TSH
- LH/FSH
- GHRH

Back to the patient....

- GNAS gene analysis
  - Heterozygous mutation Arg 231 Cys in exon 9
- Molecular diagnosis confirms pseudohypoparathyroidism

Objective 3:

Genetics of pseudohypoparathyroidism

Tissue-specific imprinting: GNAS allele

- GNAS is expressed in all tissues, with both maternal and paternal alleles
- Renal cells only express maternal allele

Parent of Origin

- Maternal allele mutation:
  - Somatic cells (50% reduction)→AHO phenotype
  - Renal tubules→PTH resistance
    - Low Ca, high Phos, and high PTH
  - Dx: pseudohypoparathyroidism
- Paternal allele mutation:
  - Somatic cells (50% reduction)→AHO phenotype
  - Renal tubules: unaffected, no PTH resistance
    - Normal labs
  - Dx: pseudo-pseudohypoparathyroidism

Pseudohypoparathyroidism Classification

- Type 1A
  - PTH resistance, AHO, and resistance to other hormones (such as TSH)
  - GNAS deactivating mutation in maternal allele
- Type 1B
  - PTH resistance, but no AHO or other hormone resistance
  - Loss of maternal exon 1A (methylation defect)
  - Normally: maternal allele methylated and paternal allele is unmethylated
  - T1B: 2 functional “paternal” alleles→no AHO

Pseudohypoparathyroidism Classification (cont'd)

- Type 1C
  - Just like T1A, but normal GNA gene
  - Unknown genetic defect
- Type 2
  - Just like T1B, but lesion is distal to cAMP mechanism

Treatment

Treatment

- Calcitriol (1,25 OH vit D)
  - Dosing: 0.06mcg/kg/d (usually 0.5mcg 1-2x/d)
- Elemental calcium
  - 50mg/kg/d
  - Common prep: Ca carbonate (40% is elemental)
- Other associated resistant states
  - Levothyroxine is most common

Patient follow-up labs on treatment

- Serum Ca: 10.6mg/dL (8.5-10.6)
- Serum Phos: 6.3mg/dL (2.5-7.1)
- U Ca/Cr: <0.20
- Required increasing levothyroxine dosing, but ultimately euthyroid state achieved
  - Free T4: 1.62ng/dL (0.88-1.84)
  - TSH: 3.8uIU/ml (0.50-4.50)

Growth/development

- Gross motor delays→started PT
- Weight improved
  - <<3rd%ile→50th%ile (and tracking without excessive weight gain)
- Length tracking at 5th%ile
  - Most recent interval growth velocity: 14cm/yr

Summary: Pseudohypoparathyroidism

- Presents with classic labs:
  - low Ca, high Phos, and high PTH
  - may also have other resistant states
    - most commonly, high TSH
- AHO phenotype is difficult in infants, but clearer as child develops
  - Short stature, developmental delays, round facies
  - Obesity
  - Short 3rd-5th metacarpals, SQ calcifications

Summary (cont): Pseudohypoparathyroidism

- Genetics due to inactivating mutation in GNAS maternal allele
- If inactivating mutation in paternal allele, then AHO phenotype, but normal labs: pseudo-pseudohypoparathyroidism
- Treatment:
  - Calcitriol
  - Elemental calcium

Questions?

References

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