Objectives

- Understand the basic physiology of calcium/phosphorus regulation
- Recognize causes of calcium and phosphorus derangements in infants and young children
- Describe the pathophysiology of various forms of rickets
Mineral Metabolism: A Short Course

Physiology Basics

• PTH effects
  – Bone resorption → Ca+phos release
  – Kidney
    • Tubule → Ca reabsorption, phos wasting
    • Increased Vitamin D hydroxylase activity
      – Increased calcitriol (1,25-OH Vitamin D)
  – Gut → dietary Ca absorption
  • PTH and calcitrol effect

Physiology Basics

• Summary effect:
  – Increased Ca, decreased Phos, increased calcitrol

• Triggers for PTH release
  – Hypocalcemia
  – Hyperphosphatemia
  – Calcitriol deficiency
Hypocalcemia: Etiology

- Early onset hypocalcemia
- Late onset hypocalcemia
- Hypoparathyroidism
  - The “Pseudo’s”
- Vitamin D deficiency

Hypocalcemia: Manifestations

- Infants often asymptomatic
- Neuromuscular irritability
  - myoclonic jerks
  - “twitching”
  - exaggerated startle responses
  - seizures
- Apnea, vomiting, laryngospasm

Tetany

Chvostek Sign aka. Elvis Sign

Trousseau Sign

Thank ya. Thank ya very much.
Early Onset Hypocalcemia
- 1-3 days of life
- Risk Factors
  - Prematurity (≤ 32 weeks)
  - Very low birth weight (< 1500 g)
    - Low calcium stores
    - Blunted PTH response
    - Decreased Vit D activation
    - Rapid bone growth
  - Maternal diabetes mellitus
    - Diminished PTH release

Early Onset Hypocalcemia
- Risk Factors
  - Perinatal asphyxia
    - Hyperphosphatemia from injured tissues
  - Maternal hyperparathyroidism
    - Infantile PTH suppressed
- Largely transient (1-2 weeks)

Late Onset Hypocalcemia
- ~1 week of life
- Hypomagnesemia
  - PTH resistance
- Increased phosphate load
  - Cows milk based formula
    - Rarely seen now
- Hypoparathyroidism
  - DiGeorge Syndrome
DiGeorge Syndrome

CATCH22
Cardiac, Abnormal facies, Thymic aplasia, Cleft palate, Hypocalcemia with 22q11 deletion

DiGeorge Syndrome Categories

<table>
<thead>
<tr>
<th>Phenotype category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Pharyngeal</td>
<td>Cardiovascular abnormalities</td>
</tr>
<tr>
<td></td>
<td>Craniofacial anomalies, velopharyngeal incompetence</td>
</tr>
<tr>
<td></td>
<td>Ear defects, hearing impairment</td>
</tr>
<tr>
<td></td>
<td>Thymic hypoplasia or aplasia</td>
</tr>
<tr>
<td>(2) Neurobehavioral</td>
<td>Learning disabilities</td>
</tr>
<tr>
<td></td>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td>(3) Others</td>
<td>Skeletal (craniofacial) anomalies</td>
</tr>
<tr>
<td></td>
<td>Vascular (other than aortic arch) anomalies</td>
</tr>
<tr>
<td></td>
<td>Kidney anomalies</td>
</tr>
</tbody>
</table>

Etiology of DiGeorge Syndrome

- Intrauterine toxicity
  - Maternal diabetes mellitus
  - Alcohol
  - Retinoic acid

- Genetic Defects
  - 22q11.2 - most common microdeletion
    - 22q11 FISH analysis positive in 85% of cases
DiGeorge Syndrome

- Consider in any newborn with hypoparathyroidism
  - T cell immunity analysis
  - Cardiac evaluation
- Additional endocrine features
  - Hypothyroidism
  - Growth hormone deficiency

Hypoparathyroidism: Other causes

- Surgical removal or damage of parathyroid glands
- Infiltration of parathyroid glands by iron, copper, or tumor
- Hypomagnesemia impairs PTH secretion and action
- Genetic defects

Genetic Hypoparathyroidism

- Isolated Endocrinopathy
  - Activating mutations of CaSR gene
  - PTH gene defects
  - Defective embryogenesis due to GCMB defects
- Complex syndrome
  - DiGeorge syndrome
  - Autoimmune polyglandular syndrome 1
  - Hypoparathyroidism-deafness-renal dysplasia (HDR syndrome)
Autoimmune Hypoparathyroidism

• Isolated hypoparathyroidism
• Autoimmune polyglandular Syndrome (APS type 1) (2q22.3)
  AIRE gene mutations
  – Hypoparathyroidism 93%
  – Mucocutaneous candidiasis 83%
  – Adrenal insufficiency 73%
  – Ectodermal dystrophy 75%
  – Additional components 2-40%

Timing of Major Features in APS type 1

Betterle, Greggio, and Volpato (1998) J Clin Endocrinol Metab 83:1049

Pseudohypoparathyroidism

• End-organ resistance to PTH
  – Kidney and Bone
  – Hypocalcemia, hyperphosphatemia, elevated PTH
• Effect of genetic imprinting
  – Maternally transmitted mutation (GNAS1)
Pseudohypoparathyroidism

- Albright’s hereditary osteodystrophy (AHO)
  - Round facies
  - Short stature
  - Short digits
  - Obesity
  - Developmental delay

Pseudo-pseudohypoparathyroidism

- Paternally transmitted GNAS1 mutation
  - Physical findings of AHO
  - Normal tissue response to PTH
    - Normal Ca, phosphate, PTH levels

Hypercalcemia: Etiology

- Familial hypocalciuric hypercalcemia
- Primary hyperparathyroidism
- Williams syndrome
- Hypercalcemia of malignancy
- Granulomatous disease
- Hypervitaminosis D or A
Benign Familial Hypercalcemia (Familial Hypocalciuric Hypercalcemia)

- Autosomal dominant disorder
- Can be associated with Severe Neonatal Hyperparathyroidism
- Very low urinary calcium excretion
- Inappropriate PTH secretion despite hypercalcemia.
- Typically benign natural history
- Caused by an inactivating defects in the gene encoding the calcium-sensing receptor in most patients.

Primary hyperparathyroidism

- Uncontrolled bone demineralization
- Increased enteral and renal Ca absorption
- Typically idiopathic in children
  - May be tumor-related
  - Possible defect in calcium sensing receptor

Williams syndrome

- Prevalence of 1/20,000
- Diagnosis by FISH - 7q11
- Developmental problems (IQ 50-70)
- “Cocktail party personality”
- Supravavular aortic stenosis
- “Elfin” face and dental abnormalities
Williams syndrome

• Early onset hypercalcemia
  – Etiology unclear
    • Normal PTH, Vit D levels
  – Typically transient, self-limited

Hypercalcemia of Malignancy

• Complicates 10-20% of cancer
• Acute, symptomatic and severe
• Malignancy usually obvious
• Causes
  – PTHrP (parathyroid related protein)
  – Calcitriol (ectopic conversion)
    • Also seen in granulomatous disease
  – Direct bone invasion

Vitamin D and Vitamin A Intoxication

• More than 10,000 IU of vitamin D per day
  – Elevated levels of 25(OH)D (>160 ng/dl)
  – Normal levels of 1,25(OH)2D
• More than 25,000 IU of vitamin A per day
  – Carnivore liver!
  – Increases bone resorption
• Carotenemia
  – Yellow-orange skin color, sclerae remain white!
  – Not toxic
Rickets

• Bone mineralization defects of the growth plates
  – Impaired vascular extension
  – Calcium or phosphorus deficits

Rickets: Clinical manifestations

• Bone and cartilage deformities
• Age-dependent skeletal defects
  – Infant: forearms, distal tibia
  – Toddler: genu varum
  – Older child: genu valgum
• Rachitic rosary
• Delayed fontanelle closure
• Bone pain

Rickets: Clinical manifestations

• Extraskeletal
  – Enamel hypoplasia
  – Decreased muscle tone
  – Seizures (hypocalcemia)
  – Infection risks
Rickets: Pathophysiology

- Hypocalcemia
  - Nutritional deficiency
    - Vitamin D
    - Calcium
  - Vit D dependent
  - Vit D receptor mutation
  - Renal osteodystrophy
- Hypophosphatemia
  - X-linked
  - With hypercalciuria

Vitamin D deficiency

- Decreased dietary intake/production
  - Breast-fed, low sun exposure
- Decreased hepatic hydroxylation
  - Liver disease
  - P450 activation increased hydroxylation and catabolism
- Decreased renal hydroxylation
  - Chronic kidney disease

Does Breast Feeding Cause Rickets? Comparison of Nutrient Values

<table>
<thead>
<tr>
<th></th>
<th>Breast milk</th>
<th>Cow’s milk</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium mg/L</td>
<td>344</td>
<td>1370</td>
<td>533</td>
</tr>
<tr>
<td>Phosphorous mg/L</td>
<td>144</td>
<td>910</td>
<td>399</td>
</tr>
<tr>
<td>Vitamin D IU/L</td>
<td>12-60</td>
<td>5-40 (400 IU/qt)</td>
<td>400</td>
</tr>
</tbody>
</table>
Thinking then (2003)

Clinical Report

Prevention of Rickets and Vitamin D Deficiency: New Guidelines for Vitamin D Intake

AMERICAN ACADEMY OF PEDIATRICS

Current AAP recommendations
- 400 Int. Units/day
- All breastfed infants as early as the 1st week of life
- Any child with low dietary Vitamin D and low sunlight exposure

And Thinking now (2008)

- In 2010, Institutes of Medicine
  - 600 Int. Units/day for ages 1-18
  - No AAP response yet

Rickets: Calcium deficiency

- Less common in US
- Typically normal levels of 25-OH Vit D
  - Elevated 1,25-OH Vitamin D
- Readily treated with standard calcium supplements (1000mg/day)
Rickets: Vitamin D dependent (Type I)

- 1-alpha-hydroxylase deficiency
  - Chromosome 12q14
  - 1,25-OH Vit D deficiency
  - Normal 25-OH Vit D levels
- Skeletal manifestations early (1st yr)
- Severe hypocalcemia (tetany)
- Rx: Calcitriol (1,25-OH Vit D)

Rickets: Hereditary Vit D Resistant

- Vitamin D dependent rickets Type II
- End organ resistance to vitamin D
  - Mutation in vitamin D receptor
- Autosomal recessive
  - Very rare (<50 families identified)
- Phenotype varies widely
- Rx: high doses of calcitriol
  - Severe cases require long-term Ca infusions

Rickets: Renal Osteodystrophy

- Phosphate accumulation from decreased glomerular filtration
- Decreased vitamin D hydroxylation
  - Hypocalcemia
- Triple trigger for PTH release
  - Often dramatic hyperparathyroidism
Rickets: Hypocalcemia

Rickets: Hypophosphatemic

- Hereditary hypophosphatemic rickets
  - "Vitamin D resistant rickets"
  - Renal phosphate wasting
- X-linked, autosomal dominant, autosomal recessive

Rickets: Hypophosphatemic

- X-linked dominant
  - 1/20,000 births
  - Chromosome Xp22 = PHEX gene
    - Peptidase – degradation of FGF-23
    - FGF-23 inhibits renal absorption of phosphorus
    - Skeletal defects when weight-bearing
    - No gender differences
Rickets: Hypophosphatemic

• X-linked dominant
  – Labs:
    • Normal calcium
    • Normal+ PTH
    • Normal– 1,25-OH Vit D
      – Abnormal!
  – Rx:
    • Oral phosphorus and calcitriol

Rickets: Hypophosphatemic

• Autosomal dominant
  – Activating mutations of FGF-23 gene
    • Inhibits renal absorption of phosphorus
• Autosomal recessive
  – Mutation in DMP-1 gene
  – Increased FGF-23 expression
• Tumor induced Osteomalacia
  – Tumor production of FGF-23

Rickets: Hypophosphatemic

• Hypophosphatemic rickets with hypercalciuria
  – Mutations in Na-Phos transporter
  – Appropriately elevated 1,25-OH Vit D levels
    • Hypercalciuria
    • Increased intestinal Ca absorption
Rickets: Hypophosphatemic