Neonatal calcium disorders

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November 3, 2016

Neonatal calcium disorders: objectives

- Review physiology of calcium regulation
- Discuss causes and management of neonatal hypocalcemia
- Define causes of hypercalcemia and discuss management strategies

Introduction

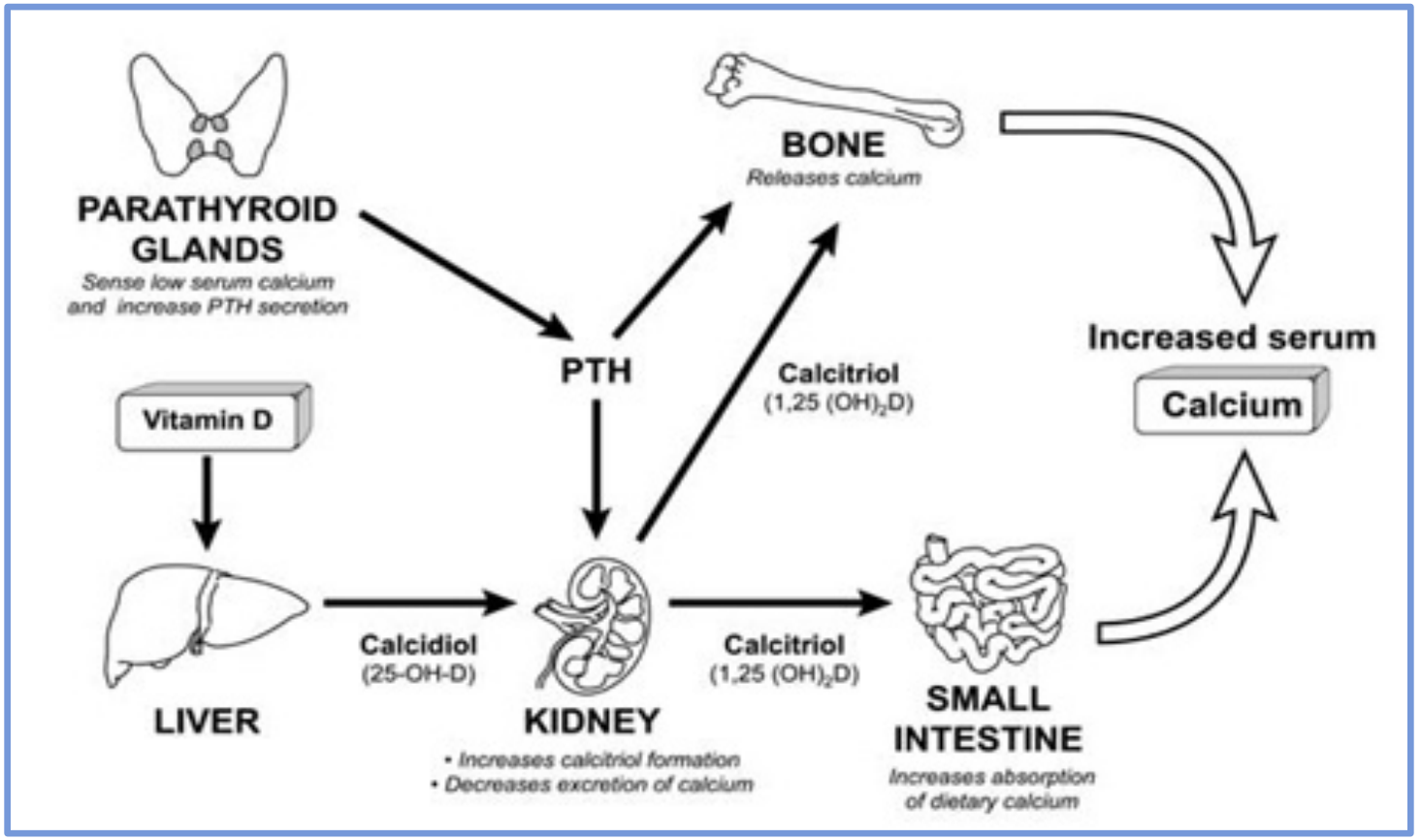
- Adequate extracellular calcium concentration needed to sustain normal physiological processes
  - Bone formation & turnover
  - Muscle contractility
  - Neuron excitability
  - Blood clotting
  - Cellular metabolism

- Extracellular calcium levels set in narrow range by regulatory “calciotropic” hormones

Calcium physiology

- Calcium is one of most abundant minerals in body
  - >98% mineral salts in bone reservoir
  - <2% soluble form
    - Bone remodeling
    - Intestinal absorption
    - Renal reabsorption
- Calcium forms in serum
  - 30-50%: Protein bound (albumin)
  - 5-15%: complex with anions (phosphate)
  - 40-50%: ionized, metabolically active

Hormonal Regulation of serum Ca



Net effect:
PTH: ↑ Ca ↓ Phos
Vitamin D: ↑ Ca ↑ Phos

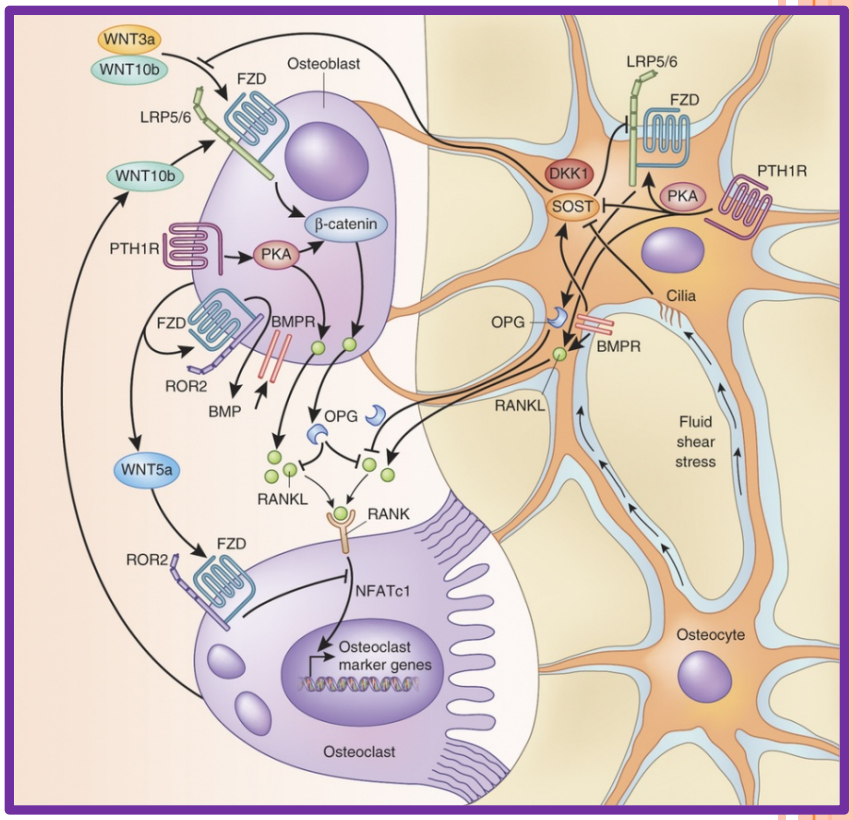
PTH EFFECTS

- Action mediated through **PTH1R** on **osteoblasts** and **kidney**

- Osteoblasts:
  - Stimulates IL-6 secretion which promotes osteoclast differentiation
  - Stimulate production of RANKL and inhibit Osteoprotegerin (OPG)
  - Promotes calcium mobilization

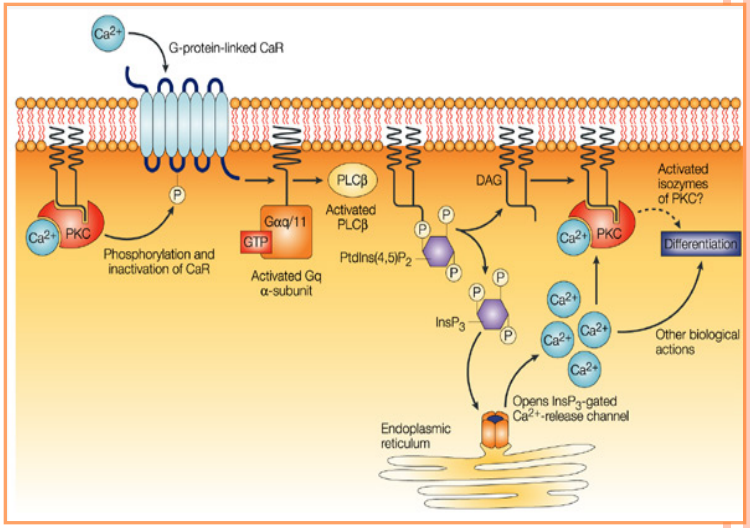
- Renal tubule
  - Activation of 1-α-hydroxylase
  - Increases calcium resorption
  - Phosphaturia

- GI tract:
  - Indirectly increases Ca and Phos absorption via calcitriol

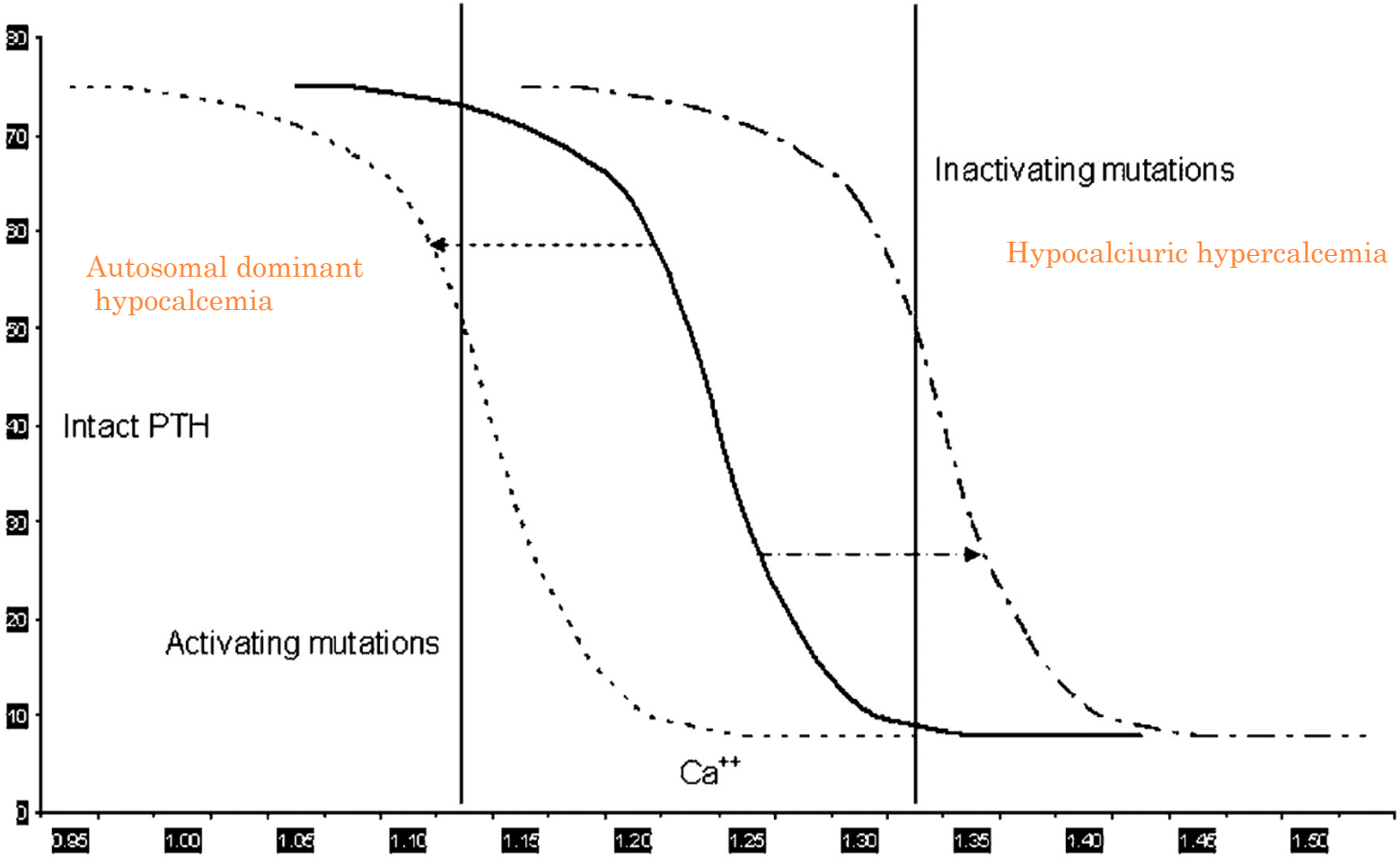


Calcium Sensing Receptor

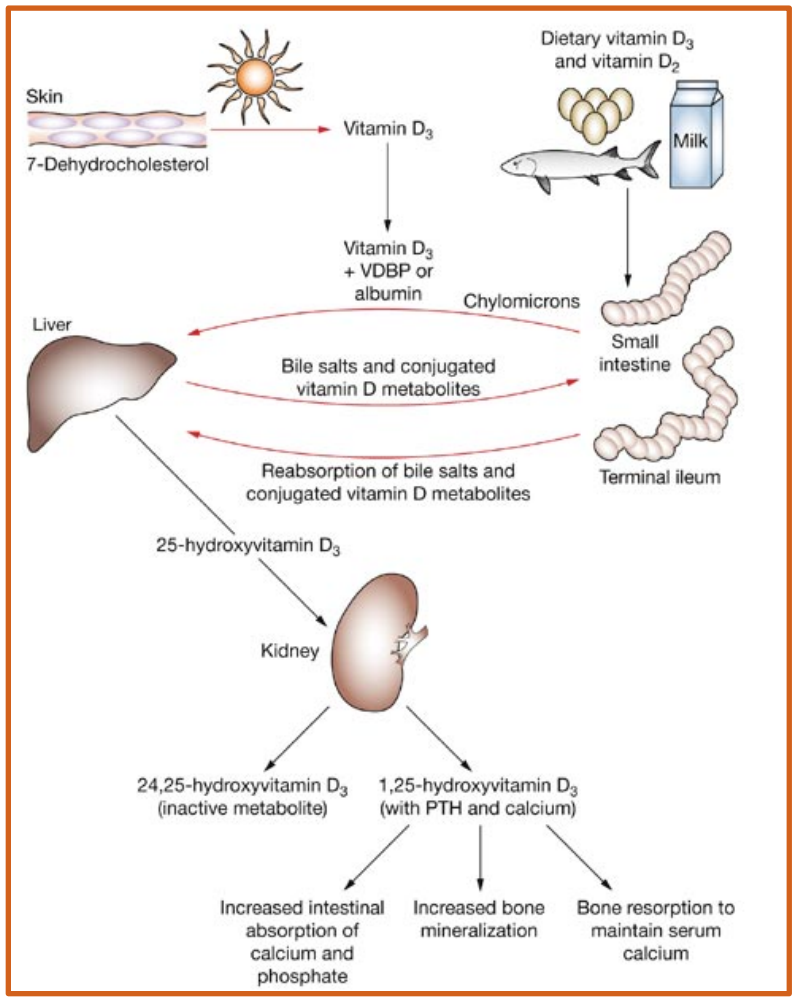
- Transmembrane G-protein coupled receptor expressed in chief cells, renal tubule, bone, brain and GI tract
- Extremely sensitive to small percent changes in ionized Ca concentration
- Affinity determines Ca setpoint
- Activation of CaSR inhibits PTH secretion
- Activation of CaSR in renal tubule inhibits calcium reabsorption



Effects of CaSR mutations on PTH-Ca curve



Vitamin D



- **Effects mediated through VDR**
  - **Nuclear receptor** which interacts with retinoic acid X receptor
  - Binds to vitamin D response elements
- **Kidney**
  - Potentiates action of PTH in increasing calcium absorption
  - Feedback inhibition of 1α-hydroxylase & activates 24-hydroxylation
- **Bone**
  - Stimulates osteoblast production of factors promoting osteoclast activity
  - Role in coordinating bone remodeling units through regulation of RANKL/OPG
- **Intestine**
  - Major determinant of calcium reabsorption
- **Parathyroid**
  - Feedback inhibition of PTH release

Physiology is fun!!!

Fetal calcium metabolism

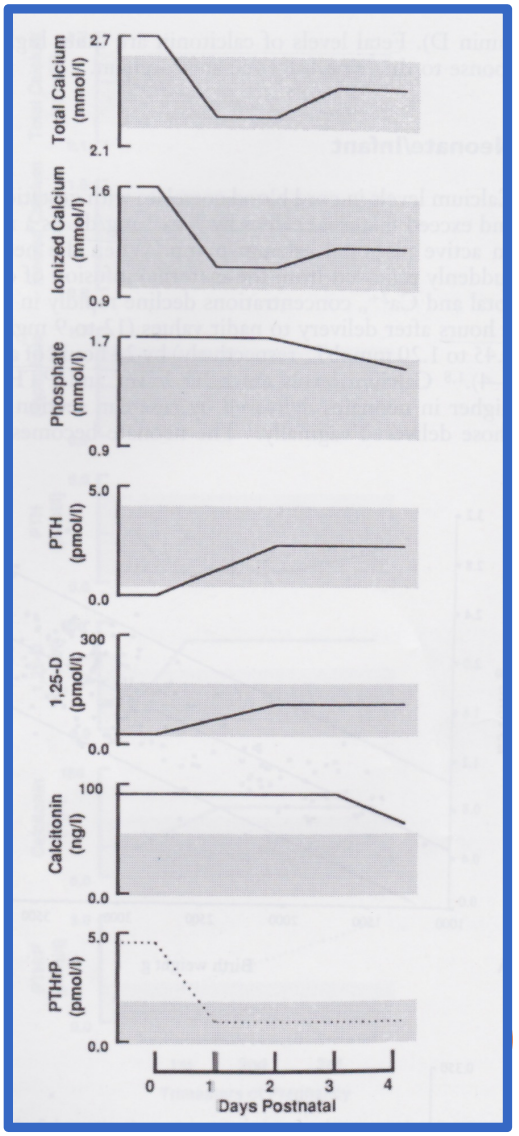
- Development of fetal skeleton is dependent on sufficient maternal supply of calcium
- Active transfer of calcium from mother to fetus
  - Fetal/maternal total calcium concentration: 1.4:1
- Adaptations during gestation:
  - Increased maternal calcitriol concentrations to 2x pregravid state
    - Increase in intestinal calcium absorption
    - Maternal BMD does not change significantly in normal pregnancy
  - Production of PTHrP by placenta and other fetal structures
    - PTHrP acts on unique placental receptor and regulates fetal calcium transfer

Fetal calcium metabolism

- Fetal PTH is low relative to maternal and postnatal levels
  - Fetal parathyroid has capacity to produce PTH in response to hypocalcemia
- Fetal calcitriol levels are low
  - Bone mineralization is independent of this hormone
- Fetal calcitonin levels are higher than adult normal range
  - Possibly serves to inhibit bone reabsorption in fetus

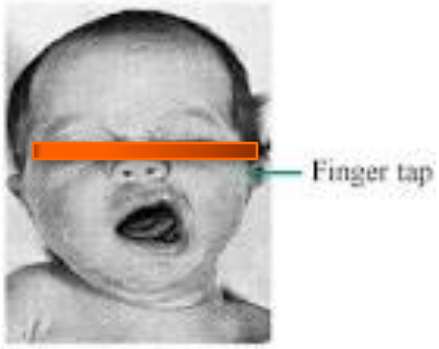
Neonatal changes in Calcium metabolism

- At birth, maternal calcium supply interrupted and PTHrP synthesis diminished
- Rapid fall in calcium concentration over first 24-48 hours
  - PTH and calcitriol increase to adult normal range by 3-4 day of life
  - Calcitonin levels decrease
- Neonate adapts to interruption in maternal calcium supply
  - Responsiveness of renal tubule to PTH increases



Hypocalcemia

- Total serum Calcium
  - < 7 mg/dl in preterm infants
  - <8 mg/dl in term infants
  - <8.8 mg/dl in children



- Clinical manifestations in neonate
  - Irritability or jitteriness
  - Lethargy
  - Feeding poorly
  - Cardiac: tachycardia, prolonged QTc
  - Apnea
  - Cyanosis
  - Seizures
  - Premature infants more likely to have subtle manifestations
    - Asymptomatic
  - Positive Chvostek and Trousseau signs uncommon in neonates

Etiology of Neonatal hypocalcemia

- Early (First 3 DOL)
  - Maternal insulin dependent diabetes
  - Prematurity, SGA
  - Birth asphyxia
  - Toxemia of pregnancy
  - Transfusion (citrated blood products)
  - Hypomagnesemia
  - Sepsis
  - Maternal hyperparathyroidism
- Late (DOL 5-10)
  - Hypoparathyroidism
    - DiGeorge Syndrome
    - CaSR activating mutations
    - Familial hypoparathyroidism
    - Pseudohypoparathyroidism
  - Vitamin D deficiency
    - Nutritional
    - Deficient 1 α-hydroxylase activity
    - VDR mutation
  - Ingestion of high phosphate milk
  - Nutritional calcium deficiency
  - Hypomagnesemia
  - Acute/Chronic Renal insufficiency
  - Transfusion
  - Diuretics (furosemide)

Early neonatal hypocalcemia

- Occurs in first 72 hours of life
- Common with prematurity, LBW, birth asphyxia, gestational or insulin dependent diabetes
- Due to suppressed PTH release, prolonged calcitonin secretion or hypomagnesemia.
- Prematurity
  - Preterm neonates have postnatal decrease in calcium that occurs earlier and is more exaggerated
  - Inverse relationship between frequency of hypocalcemia vs BW and GA
    - >50% of preterm VLBW infants may develop hypocalcemia
  - Mechanisms
    - Delayed responsiveness of parathyroid gland
    - Delay in phosphaturic action of PTH
    - Prolonged increase in circulating calcitonin
    - Rapid accretion on calcium into bone in VLBW infants

Early neonatal hypocalcemia

- IDM
  - Hypomagnesemia>Functional hypoparathyroidism
  - Occurs in 50% of infants
  - Incidence may be reduced glycemic control
- Hyperbilirubinemia/Phototherapy
- Therapy with compounds that complex with calcium
  - Citrated blood products
  - Phosphates
  - Fatty acids
- Alkalosis
  - Shifts ionized calcium to protein bound compartment

Early Neonatal hypocalcemia

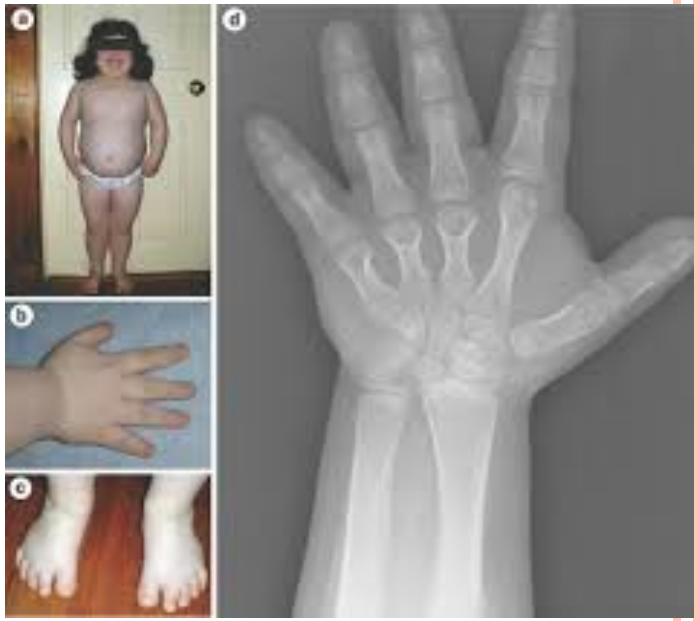
- Maternal hyperparathyroidism
  - Hypercalcemia in mother>fetal hypercalcemia>inhibits fetal PTH gland function
  - Transient as PT glands increase responsiveness
  - Usually occurs in first 3 weeks of life, but can occur as late as 1 year
  - Can be the presenting manifestation of maternal hyperparathyroidism
- Maternal intake of high doses of calcium can result in PTH gland suppression

Late Neonatal hypocalcemia

- Hypoparathyroidism
  - Synthesis of defective PTH
  - DiGeorge/Velocardiofacial syndrome
    - Up to 30% may have hypoparathyroidism
      - May gradually resolve over time, and reappear at older age
    - Infants/children with apparently isolated hypoparathyroidism have deletions of chromosome 22q11.2
  - Activating mutations of CaSR
    - Reduces extracellular calcium concentration necessary to elicit PTH
    - Usually mild, asymptomatic hypocalcemia with hypercalciuria
    - May be autosomal dominant or sporadic

Late neonatal hypocalcemia

- Pseudohypoparathyroidism
  - Impaired responsiveness to PTH
  - Heterozygous inactivating mutation of GNAS1 that encode αsubunit of Gsα
  - Resistance to other G protein coupled receptors
- Vitamin D deficiency
  - Nutritional deficiency may occur in offspring of mothers with Vit D deficiency
  - VDDRI
    - 1-α hydroxylase deficiency
  - VDDRII
    - Abnormal Vit D receptor
    - Often seen with alopecia

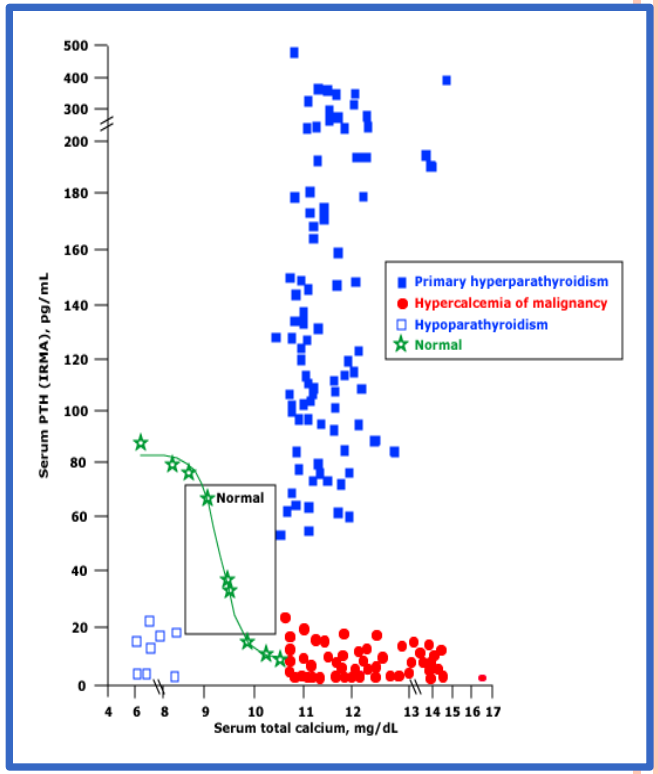


LATE NEONATAL HYPOCALCEMIA

- Excessive ingestion of phosphate
  - Modified cow's milk formulas or evaporated milk
  - Phosphates form poorly soluble salts with calcium and limit absorption

Diagnosis of hypocalcemia

- Laboratory assessment:
  - Total and ionized calcium, magnesium, phosphorus
  - PTH
  - Spot urine Ca:Cr
  - Electrolytes including BUN & Cr
  - Acid-base status
  - Vitamin D metabolites
- Lab evaluation of mother if hypocalcemia unexplained



Acute Treatment of neonatal hypocalcemia

- Rapid treatment of symptomatic neonate
- Asymptomatic
  - Total calcium < 7 mg/dl in term infants
  - Total calcium <6 mg/dl in preterm infants
- IV infusion calcium gluconate (10%)
  - 2ml/kg (18mg elemental Ca/kg) bolus over 10 min while monitoring EKG for bradycardia
  - Central IV access preferable (chemical burns)
- Continous infusion of Ca Gluconate may be necessary to maintain low nl calcium (preferable over bolus)
  - 50-80mg/kg/24 hrs
  - Decrease by 50% every 24 hours over 2 days, then discontinue

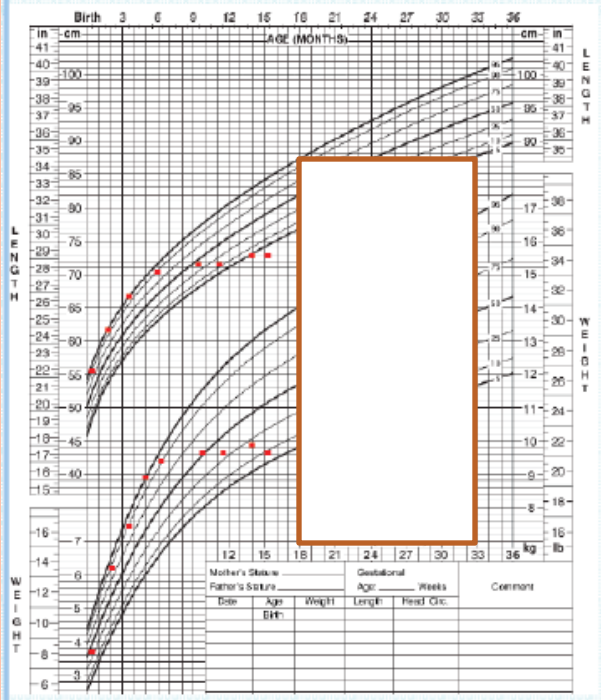
Chronic management of hypocalcemia

- Transition to oral calcium therapy as soon as possible
  - 25-100mg el ca/kg/day divided q4-6hrs
  - Monitor serum Ca, Ca X Phos, and U Ca:cr
- Vitamin D is integral part of therapy in all forms of hypoparathyroidism
  - **Calcitriol** has short-half life and high activity
  - Calcitriol dose: 20 to 60 ng/kg/day
  - Ergocalciferol/Cholecalciferol used for vitamin D deficiency
- Use lower starting dose and titrate to maintain serum calcium 8.5-9.0 mg/dl
- Monitor for hypercalciuria and nephrocalcinosis

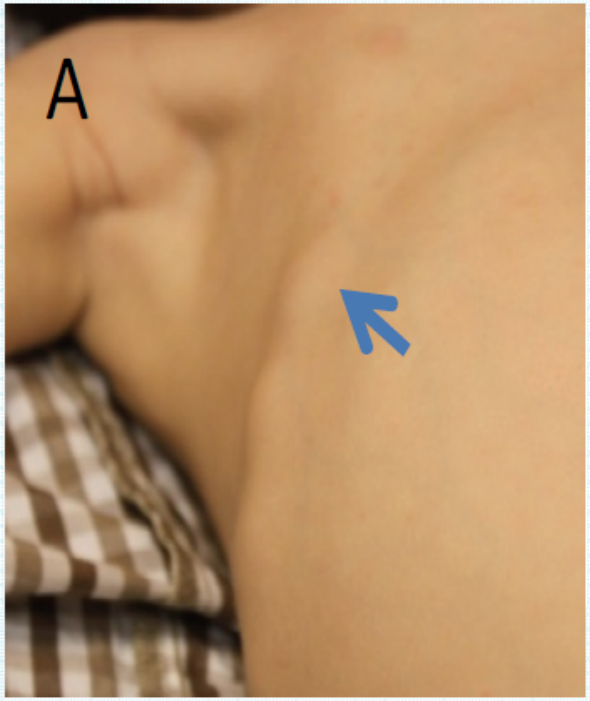
Case 1

- 16 mo caucasian male with gross motor delay
- Term AGA; uncomplicated pregnancy
- Appeared normal at birth: normal tone and muscle mass
- At 8-9 months, pt began to regression of motor milestones.
  - Progressive hypotonia & weakness
  - At 16 mo: unable to sit or push up from prone position
- Frequent respiratory infections
  - 2 episodes pneumonia; 4 episodes OM

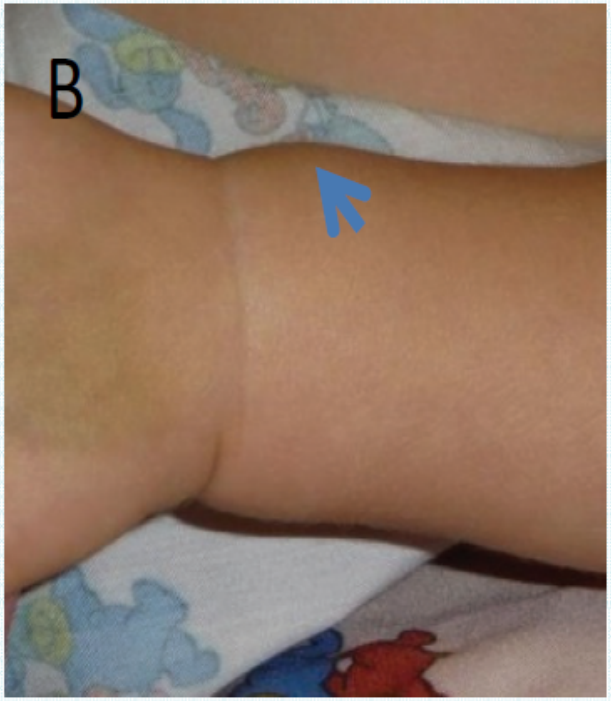
Case 1



Growth Chart



A. Rachitic Rosary



B. Widened Wrist

Case 1

Laboratory

Serum calcium: 5.1 MG/DL (9.0-11.0)

Serum phosphorous: 3.7 MG/DL (4.5-6.7)

Serum magnesium: 1.5 MG/DL (1.6-2.2)

Alkaline phosphatase: 2459 U/L (145-320)

PTH: 410 PG/ML (12-72)

25 $(OH)_2$ vitamin D: 67 NG/ML (25-80)

1, 25 $(OH)_2$ vitamin D: 32 PG/ML (24-86)

Serum sodium: 138 MMOL/L (135-145)

Serum CO_2: 17 MMOL/L (22-30)

Serum chloride: 112 MMOL/L (98-107)

BUN: 5 MG/DL (5-17)

Creatinine: 0.18 L MG/DL (0.20-0.50)

Albumin: 4.5 G/DL (3.5-5.0)

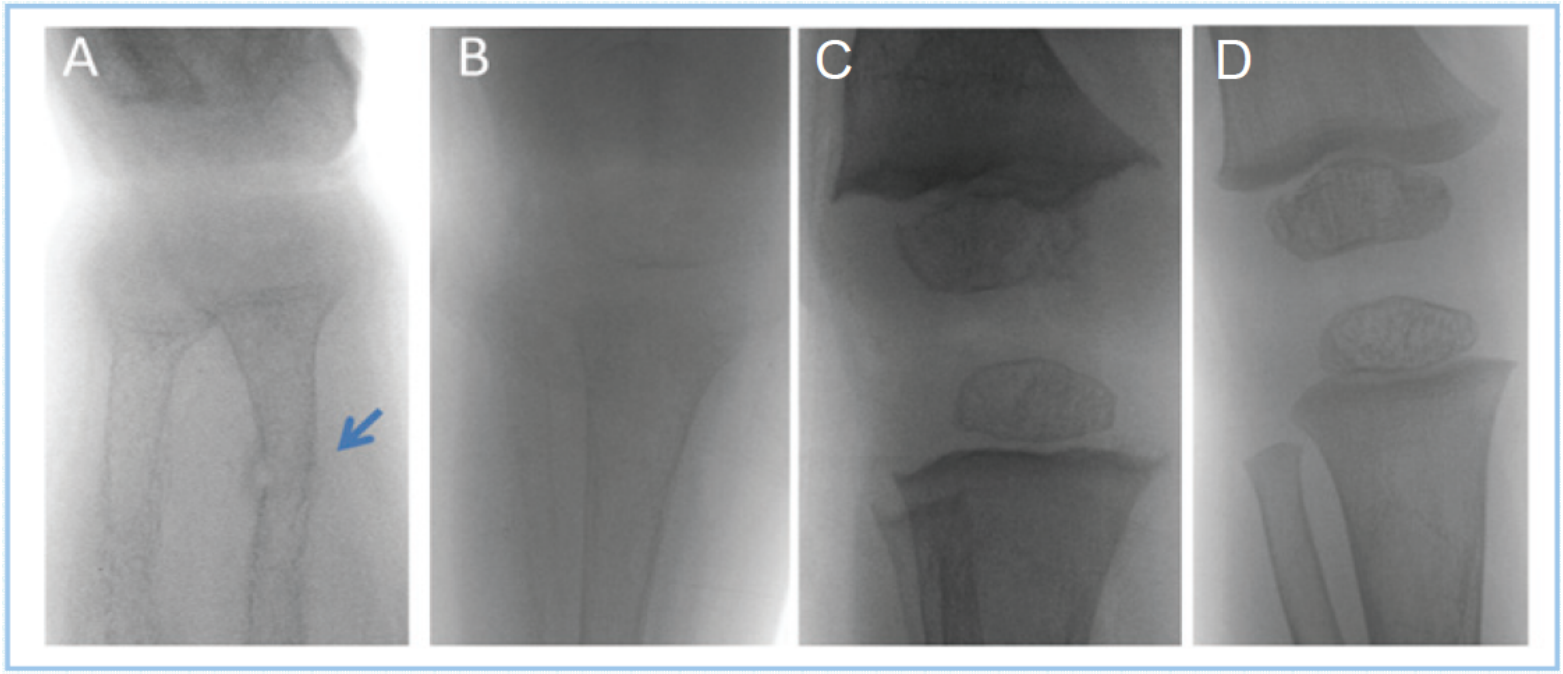
AST: 40 U/L (20-60)

ALT: 9 U/L (5-45)

Urine: elevated glutaric and succinic acid levels and generalized aminoaciduria

Urine PH: 7.0

Radiologic findings



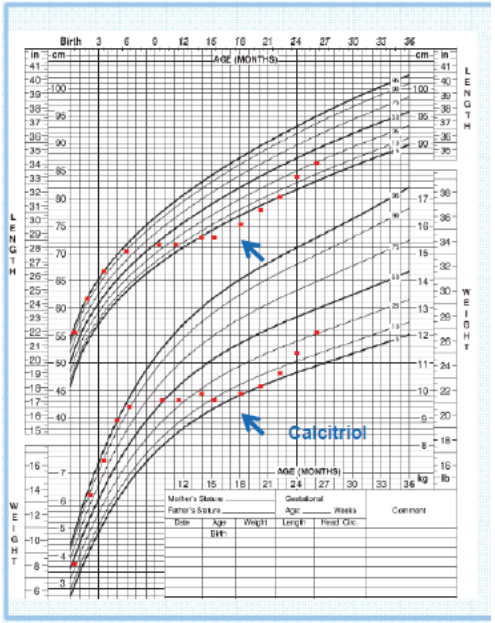
A and B: Before treatment: severe osteopenia and radial fracture (arrow). There were also healing fractures of the radius and ulna bilaterally as well as fractures of the second and third metatarsal on the left and the second, third, fourth, and fifth metatarsal on the right. Also note widened, frayed and irregular metaphysis, small epiphyses were small for age. and delayed ossification of the proximal femoral epiphyses and of the carpal bones. **C:** After 5 months treatment. **D:** After 8 months treatment.

Diagnosis

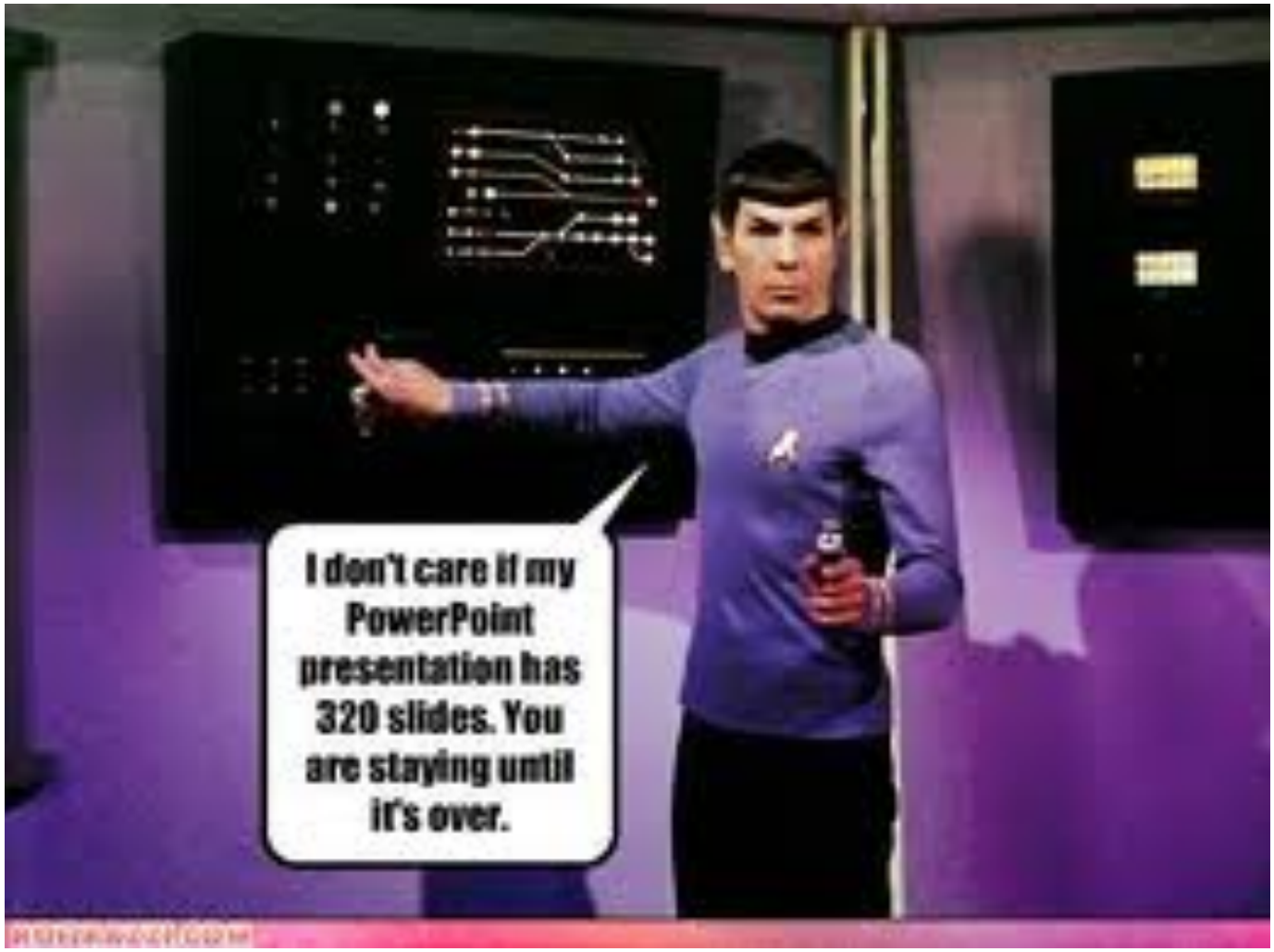
- Vitamin D dependent rickets type 1 (1- α hydroxylase deficiency)

- Treatment:
  - Calcitriol
  - Calcium

- Dramatic improvement
  - Muscle strength & motor milestones
  - Growth
  - Aminoaciduria resolved 2mo after PTH normalized
  - Decreased respiratory infections



Growth Chart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Neonatal hypercalcemia

- Hypercalcemia uncommon in neonates:
  - Serum Calcium >11mg/dl (2.75 mmol/L)
  - iCa >5.6 mg/dl (1.4 mmol/L)
- Results from
  - Increased intestinal or renal absorption
  - Increased bone turnover
  - Iatrogenic causes
    - Low phosphorus diet
- Signs/Symptoms
  - Anorexia/GI reflux/emesis
  - Polyuria
  - Lethargy or irritability
  - Cardiac arrhythmia/HTN
  - Hypotonia
  - Seizures

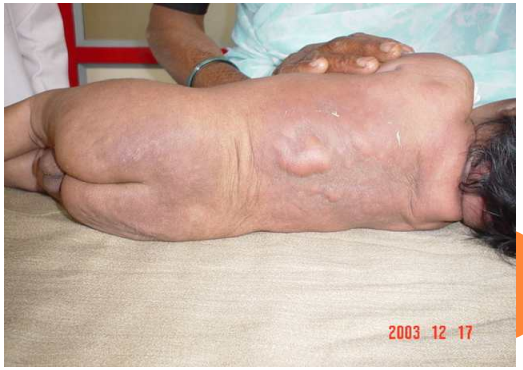
Etiology of neonatal hypercalcemia

- **Maternal illness**
  - Hypocalcemia
  - Excessive intake of Vitamin D
- **Neonatal illness**
  - Hyperparathyroidism
    - Familial
      - Familial hypocalciuric hypocalcemia
      - Neonatal Severe Hyperparathyroidism
      - Metaphyseal Chondrodysplasia (PTH1R activation)
      - Excessive secretion of PTHrP
  - Williams Syndrome
  - Idiopathic infantile hypercalcemia
  - Other:
    - Subcutaneous fat necrosis
    - Excessive intake Vit D
    - Excessive administration of calcium
    - Hypophosphatemia
    - Abnormal renal tubular function
    - Infantile Hypophosphatasia

Causes of Neonatal hypercalcemia

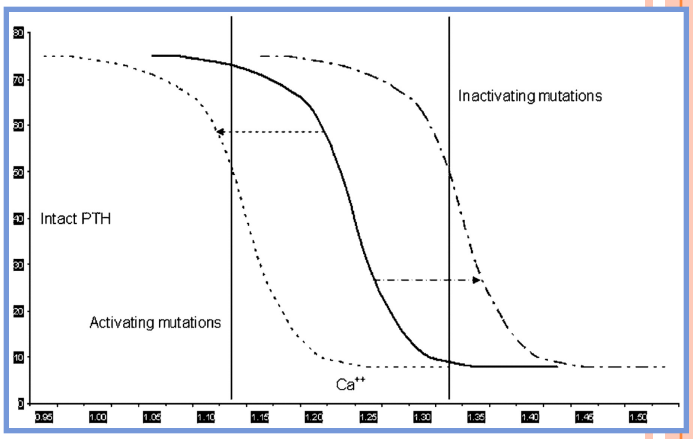
- Nutritional causes most common
  - Administration of excessive Calcium
  - Vitamin D toxicity
    - Maternal Vit D excess
  - Low phosphorus diet
    - Breast milk
    - Parenteral nutrition with insufficient phosphate

- Subcutaneous fat necrosis
  - Initial period of hypo- or normocalemia
  - Hypercalcemia can develop 2-16 weeks
    - Increased PGE and calcitriol from macrophages infiltrating necrotic lesions



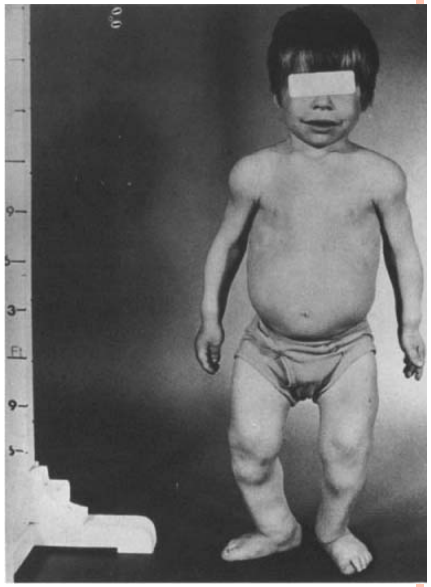
Causes of Neonatal hypercalcemia

- Parathyroid related disorders
  - Familial hypocalciuric hypercalcemia is autosomal dominant, heterozygous **inactivating** mutation of CaSR
    - Increases Ca set point
    - Mild, asymptomatic hypercalcemia (usually < 12 mg/dl)
    - Inappropriately nl PTH
    - Increased tubular reabsorption of Ca (Inappropriately low U Ca:Cr)
  - Severe Neonatal Hyperparathyroidism is homozygous inactivating mutation of CaSR
    - Severe hypercalcemia (usually >16mg/dl)
    - Can be lethal in first week of life



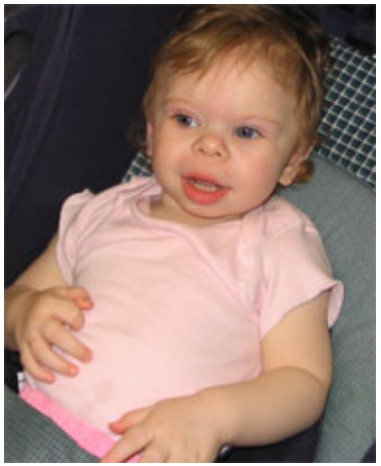
Causes of Neonatal hypercalcemia

- Parathyroid related disorders
  - Transient neonatal hyperparathyroidism secondary to maternal hypocalcemia
    - Maternal hypoparathyroidism or pseudohypoparathyroidism
    - Usually resolves 2-4 weeks
  - Jansen syndrome (metaphyseal dysplasia)
    - Constitutively active PTH1R
    - Hypercalcemia with PTH levels undetectable
    - Often with marked short stature and deformity
    - VERY rare (20 cases reported)



Causes of Neonatal hypercalcemia

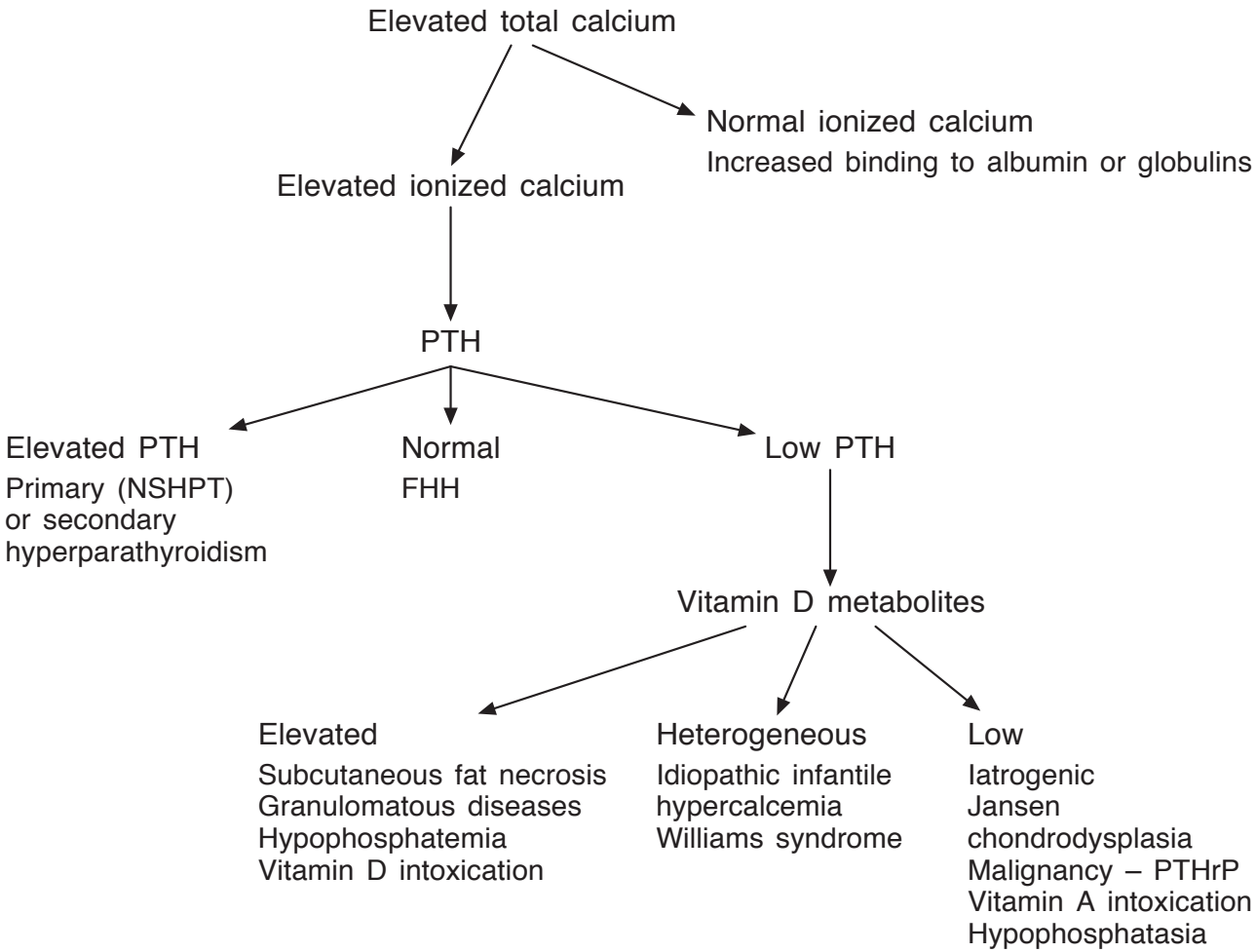
- Vitamin A excess
  - Due to retinoic acid stimulation of osteoclasts
- Adrenal insufficiency
  - Glucocorticoids inhibit calcium absorption and 1-α hydroxylase
  - Dehydration associated with adrenal insufficiency
- Williams Syndrome
  - Hypercalcemia in infancy that usually resolves
    - Mechanism unknown
  - Supravalvular AS
  - Pulmonary arterial stenoses
  - Eflin faces
  - Developmental delay
  - Renal anomalies



Hypercalcemia: Evaluation

- Total Ca & iCa
- Serum Phosphorus
- Spot urine Ca:Cr
- Intact PTH
- 25-OH Vitamin D
- 1,25-OH Vitamin D

DIAGNOSIS OF PERSISTENT HYPERCALCEMIA



Treatment

- Mild hypercalcemia (total calcium < 12mg/dl) usually does not require immediate intervention
  - Low calcium diet
- Moderate hypercalcemia (total calcium 12-13.5mg/dl)
  - Infusion of normal saline (10-20 ml/kg)
  - Loop diuretic (lasix 1mg/kg)
- Severe (total ca >14mg/dl)
  - Above measures
  - Adjuncts
    - Bisphosphonates
    - Glucocorticoids (inhibit 1-α OHase)
  - Hemodialysis if comatose

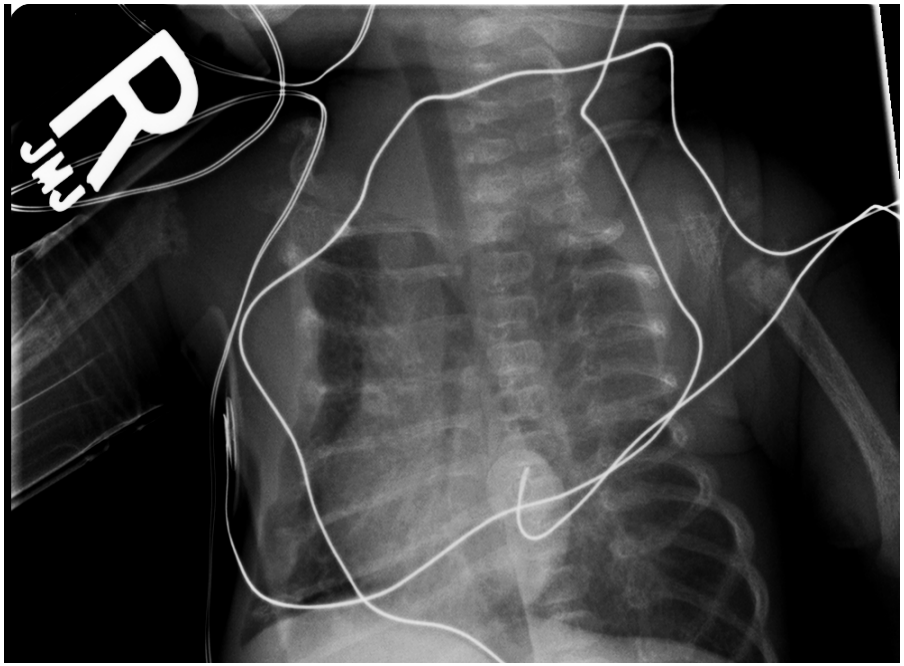
Case

- 2-month old well appearing African American male
- Incidentally found to have osteopenia and numerous healing rib fractures during a rule out sepsis workup at 2 weeks of age.
- Serum calcium 13 mg/dl (high)
- PTH 127 pg/ml (moderately elevated)
- Urinary calcium inappropriately low
- Baseline DXA showed a BMD (L1-4) of 0.131 g/cm2 (<5th percentile for Height and weight, Z-score < -2.0 S.D)
- No pertinent family history.

Biochemical Evaluation

Serum Calcium	13 mg/dl (9-11 mg/dl)
Parathyroid Hormone	127 pg/ml (12-72 pg/dl)
Urine Ca/Cr Ratio	undetectable (<0.86 mg/mg)
Magnesium	2.5 mg/dL (1.6-2 mg/dL)
Phosphorous	5.4 mg/dL (4.8-8.1 mg/dL)
Alkaline Phosphatase	610 U/L (150-420 U/L)
1,25 OH Vitamin D	142 pg/ml (22-67 pg/ml)
Total 25 OH Vitamin D	27 ng/mL (25-80 ng/mL)
Ionized Calcium	7.17 mg/dL (4.4-5.4 mg/dL)

Imaging

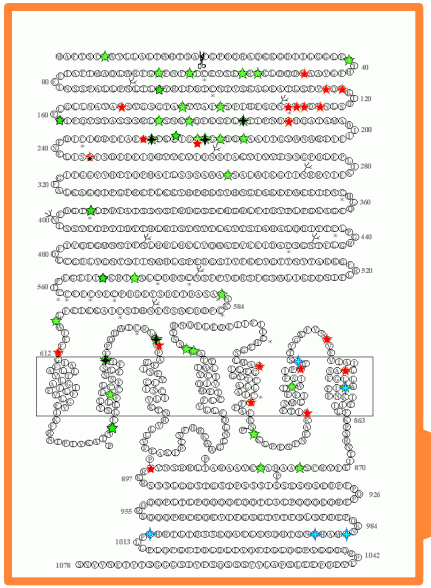


- Bones appear diffusely demineralized
- Abnormal appearance of the proximal humeral metaphysis
- Periosteal new bone associated with several ribs

Diagnosis?

- Severe neonatal hyperparathyroidism due to homozygous calcium sensing receptor inactivating mutation
  - Two single-base mutations in exon 7 associated with Familial Hypocalciuric Hypocalcemia

- Treated with IV hydration and bisphosphonates



Questions?