



Bisphosphonates and Denosumab in Fibrous Dysplasia

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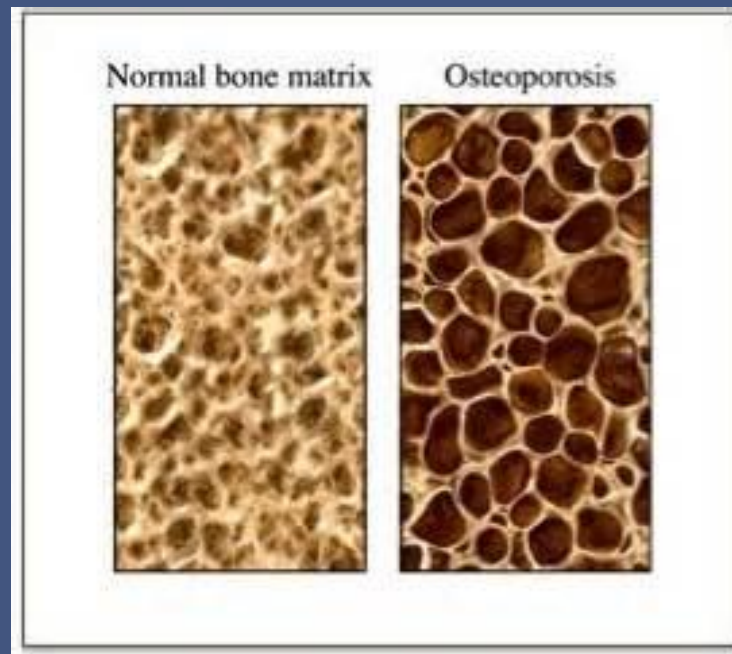
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FD Foundation Meeting 2014

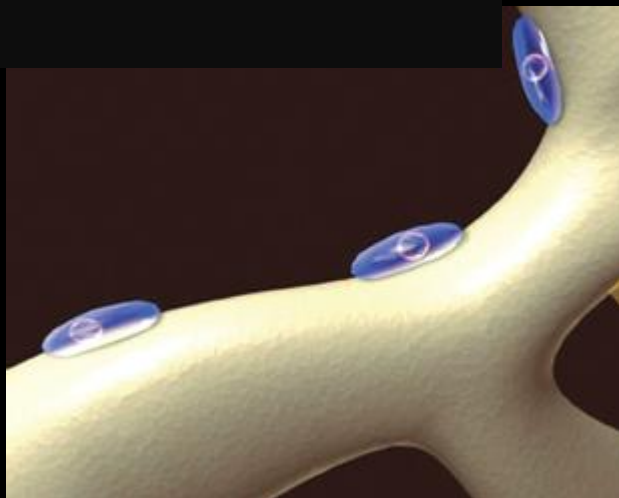
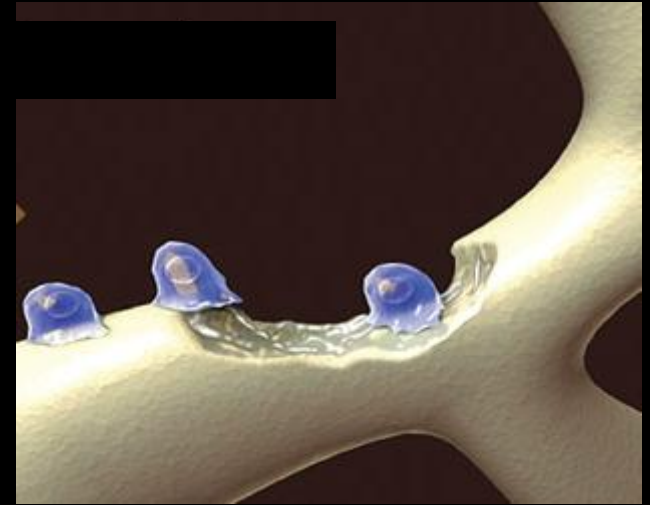
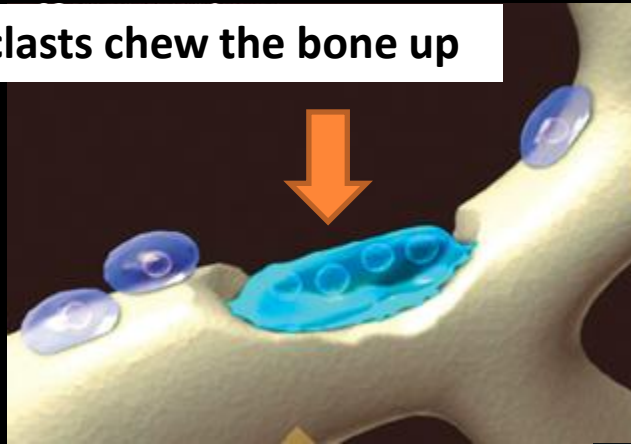
What are Bisphosphonates?

- Medications that prevent bone breakdown
- Used to treat disorders with **low bone mass** or **high bone activity**

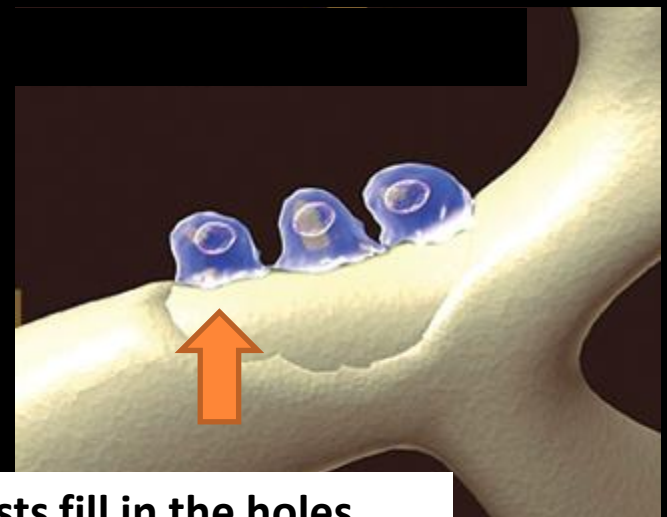


Bone Remodeling Cycle

Osteoclasts chew the bone up



Osteoblasts fill in the holes



How do bisphosphonates work?

- Taken up by bone cells and incorporated into the skeleton's matrix
- Decrease the activity of the bone resorbing cells



How do bisphosphonates work?

- Taken up by bone cells and incorporated into the skeleton's matrix
- Decrease the activity of the bone resorbing cells
 - Less bone breakdown -> denser, stronger bone



Types of Bisphosphonates

Intravenous

- Pamidronate (Aredia)
 - 3 hr infusion, ~every 3 months
- Zoledronic acid (Reclast)
 - 30 min infusion, ~every 6 months
- Ibandronate (Boniva)
 - Rapid infusion, ~every 3 months

Oral

- Alendronate (Fosamax)
 - Weekly pill
- Risedronate (Actonel)
 - Daily or weekly pill

What types of patients use bisphosphonates?

- FDA-approved for treatment of adults with:
 - Osteoporosis
 - Paget's disease
 - Bone tumors and bone metastases
 - High blood calcium levels

All other uses are “off-label”

What about kids?

- Different factors to consider
 - Kids' bones are growing
 - Kids have different kinds of bone diseases than adults
 - There are far fewer studies conducted in kids



Bisphosphonates in Kids

- Most major studies conducted in kids with Osteogenesis Imperfecta (Brittle Bone Disease)
- No significant effects on growth or bone shape
- Helpful for pain
- Probably decrease fractures in OI





Side Effects of Bisphosphonates

- **Flu-like symptoms** after first 1-2 doses
 - Temporary, usu manageable with Tylenol/Motrin
- **Low blood calcium**
 - Make sure to eat dairy
 - Take vitamin D supplement; consider calcium supplements
- **GI disease** (reflux, ulcerations): Oral forms only
 - Can be severe!
 - STOP drug if developing symptoms

Osteonecrosis of the Jaw

- Typically adult cancer patients on steroids, given long-term high dose IV infusions, after dental procedures
- No known cases in kids or adolescents
- Few cases in patients with fibrous dysplasia
- Complete planned dental work prior to starting

Bisphosphonates in Fibrous Dysplasia

- Various case reports
 - Most show improvement in pain
 - Conflicting reports about effects on FD lesions
- One clinical trial in alendronate (oral form):
 - No improvement in pain
 - No change in FD lesions

Start of Study



After 2 years of treatment



Alendronate-Treated Patient

Placebo-Treated Patient (no active drug)



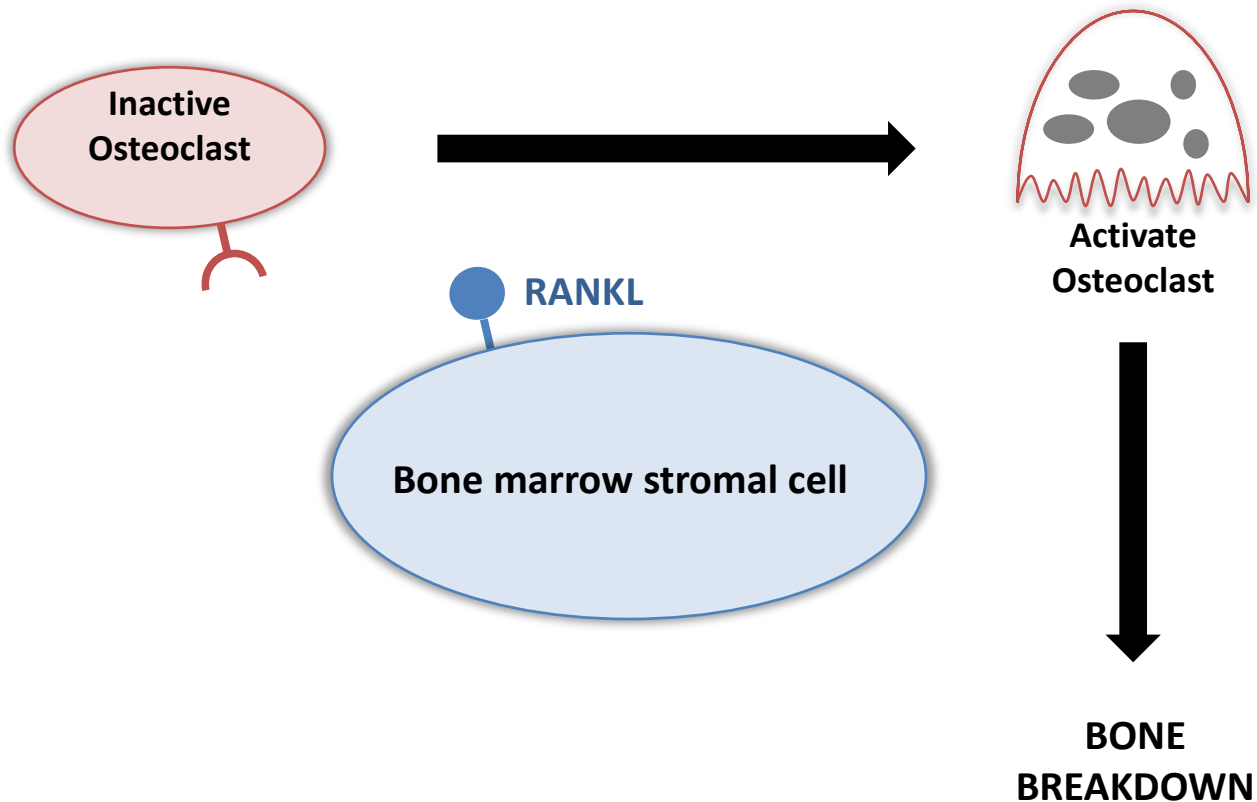
NIH Experience with Bisphosphonates

- Only use for pain
- IV bisphosphonates (Zoledronate, Pamidronate) relieve pain in most, but not all patients
- Oral bisphosphonates do not relieve pain
- Bisphosphonates are better at relieving body pain than head pain
- It may take more than one infusion to start working
- Pain comes back at different intervals for different patients -> dose as needed
- Try to use lowest dose at lowest frequency to treat pain

Denosumab (Xgeva[®], Prolia[®])

- Antibody that binds and inhibits RANKL
- Similarities to bisphosphonates
 - Also inhibits bone breakdown
 - Also FDA-approved for adults with osteoporosis and bone tumors
- Key differences to bisphosphonates:
 - More potent
 - Shorter-acting (6 months vs >10 years)
 - Much less data

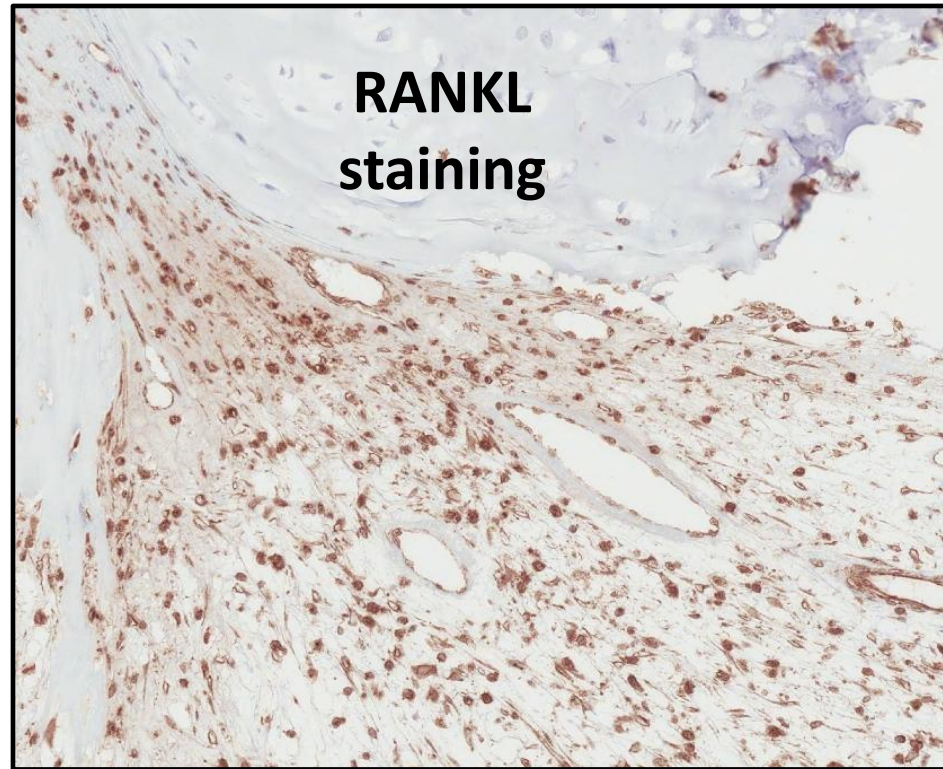
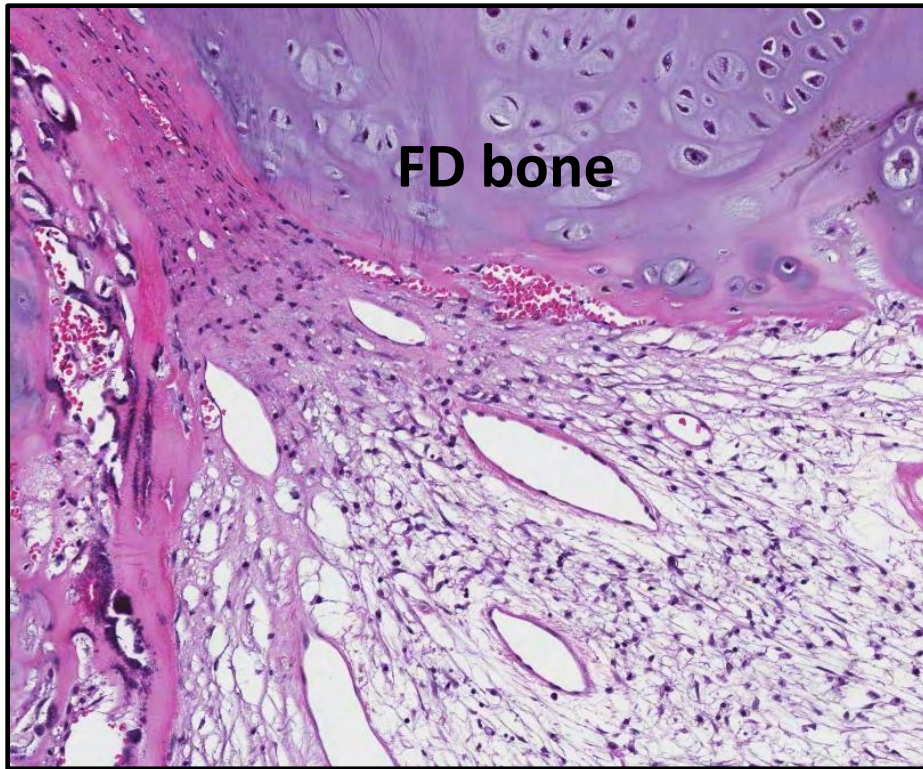
RANKL turns on the cells that break down bone



Denosumab PREVENTS this process

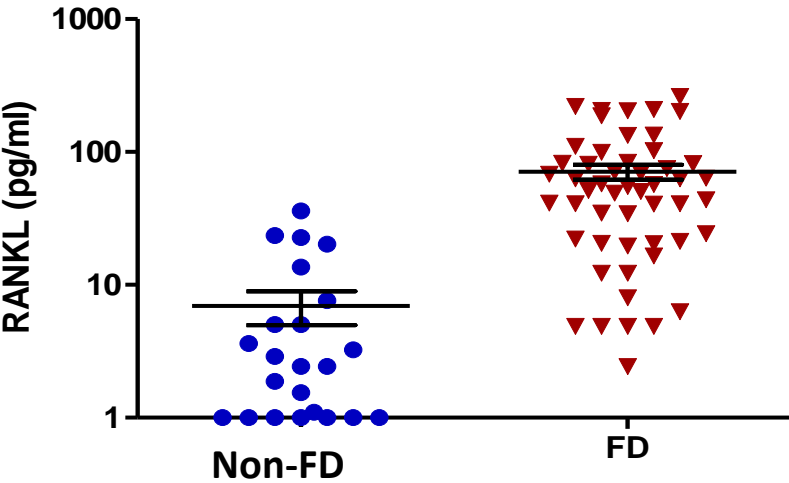
Why are we talking about denosumab
in FD?

RANKL is found in bone from FD patients

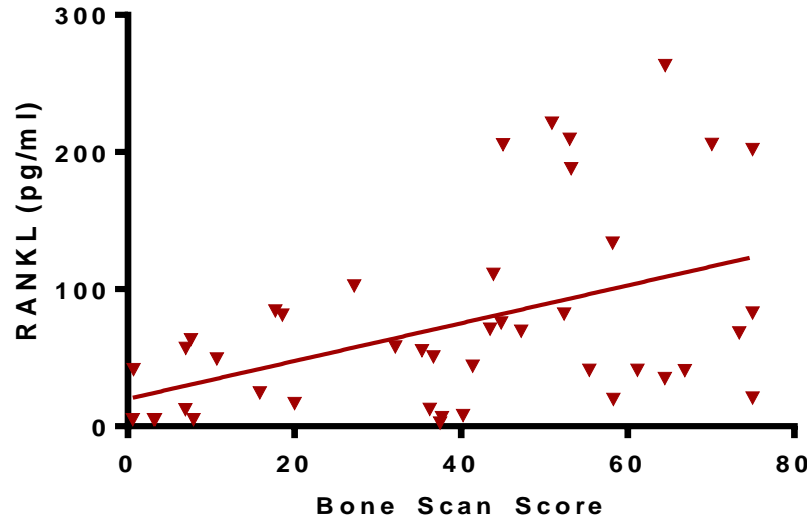


RANKL is found in blood from FD patients

RANKL levels are higher in FD patients than in non-FD patients



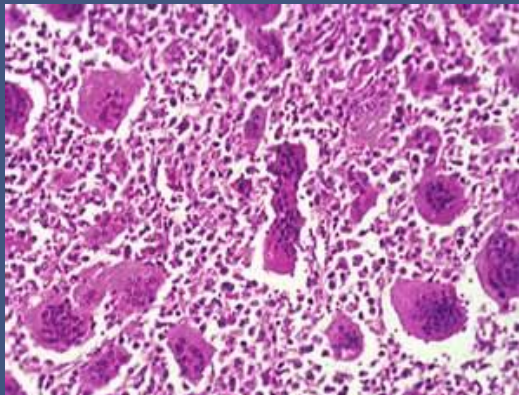
RANKL levels are higher in patients who have more FD



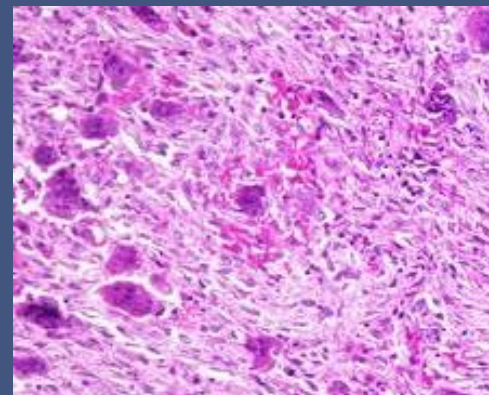
Denosumab is effective for treatment of Giant Cell Tumors

- Bone lesion involving the same type of cell as FD (bone marrow stromal cell)
- Tissues has very similar appearance to FD

Giant cell tumor



FD



Denosumab and FD

- 3 patients treated at the NIH, 3 additional patients in published reports
 - Improvements in pain
 - Mild-to-severe abnormalities in blood calcium and phosphorus
 - Effect on FD lesions not known

Denosumab and FD: Many Areas of Uncertainty

- Does it work?
- What dose? How frequently?
- Is it safe? What side effects might occur? How should patients be monitored?
- What happens when the drug is stopped?
 - One patient hospitalized with severe hypercalcemia
- What happens to kids?
 - Growth effects? Osteonecrosis?
 - Trial in kids with OI has recently started

Denosumab and FD: Where are we now?

- Pilot study in adults with FD planned to start at NIH in the next year
- At this time we do NOT recommend off-label use, except in very rare circumstances given by practitioners very experienced in FD

Endocrine Disorders in FD/MAS

- Precocious Puberty
- Hyperthyroidism
- GH Excess
- Phosphate wasting
- Cushing Syndrome

Findings in our MAS patients at the NIH

<u>Findings</u>	<u>Prevalence (%)</u>
Fibrous dysplasia	99
Café-au-lait	89
Precocious puberty	
male	15
female	78
Thyroid	69
Phosphate wasting	48
Growth hormone excess	18
Cushings	7

Precocious Puberty

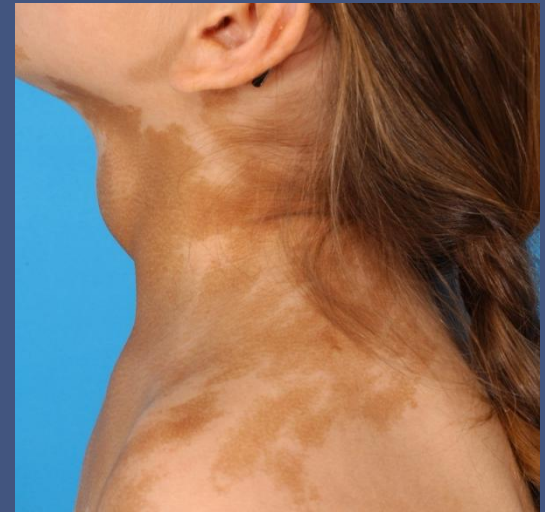
- Most common endocrine disorder in girls (~80%)
 - Transient ovarian cysts -> recurrent, relapsing course
 - In boys, steady testosterone production -> sustained course
- Goals of Treatment:
 - Prevent short stature in adulthood (primary!)
 - Prevent bleeding and sexual development
 - Prevent social and behavioral issues, patient discomfort

Precocious Puberty: Treatment

- NO surgery!
- **Letrozole**: blocks estrogen formation
- **Tamoxifen, Fulvestrant**: block estrogen action
- In boys: testostolactone, flutamide block testosterone action
- Central puberty usu occurs after several years. Treat with **Lupron** (injections or implant) to suppress the puberty

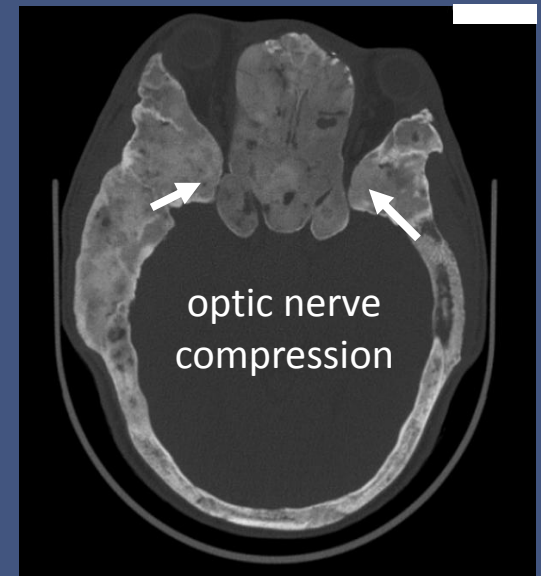
Hyperthyroidism

- Overproduction of thyroid hormone
- First-line initial treatment:
Methimazole
 - Twice daily oral medication
 - Monitor liver tests and blood counts
- Permanent treatment
 - Surgery preferred. MUST use experienced endocrine surgeon



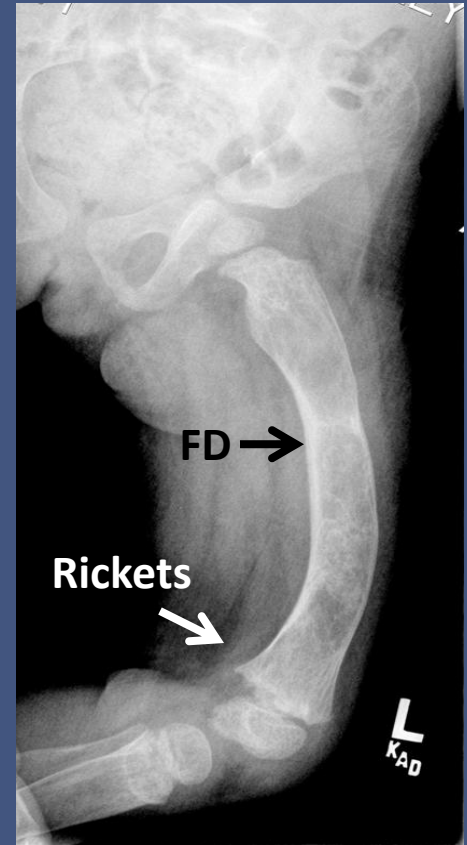
Growth Hormone Excess

- Diagnose and treat early. If untreated, increases skull FD expansion and risk of vision loss
- Medications
 - **Octreotide** (Sandostatin): intramuscular injection monthly
 - **Pegvisomant** (Somavert): subcutaneous injection daily
- Surgery
 - technically difficult
 - need to remove the entire pituitary
- Radiation
 - last resort – increased cancer risk



Phosphate Wasting

- FD overproduces the hormone FGF23 -> too much phosphate is dumped into the urine
- Increases fractures and bone pain
- Treat with oral phosphate + calcitriol
 - Must give 3-5 times a day
 - Monitor urine calcium
 - Stop medications when immobilized
- Phosphate wasting may improve or resolve with time



What initial testing should be done?

- **Thyroid:** ultrasound, blood tests (TSH, T3)
- **Phosphate:** blood and urine phosphorus levels
- **Growth hormone:** IGF-1, glucose tolerance test, MRI pituitary if needed
- **Cushings:** monitor growth and development in kids under age 3 years

Monitoring Treatment for Endocrine Disorders

- For all endocrine conditions in children:
Growth chart, Growth chart, Growth chart!
- In addition:
 - Precocious puberty: Bone age X-ray
 - Hyperthyroidism: Blood tests (TSH, T3)
 - Growth hormone excess: Blood tests (IGF-1)
 - Phosphate wasting: Blood and urine phosphorus, symptoms of pain and fatigue

Frequency of follow-up

- Depends on the issue
- Stable disease – twice a year
- Patients with uncontrolled symptoms or taking medications –every 3-4 months and as needed

Acknowledgements

SCSU

Michael Collins
Beth Brillante
Lori Guthrie
Nisan Bhattacharyya
Rachel Gafni
Andrea Burke
Mary Scott Ramnitz
Andrea Estrada
Diana Ovejero Crespo

CSDB

Pam Robey
Larry Fisher
Marian Young
Kenn Holmbeck
Sergei Kuznetsov
Natasha Cherman

SCSU Former Trainees

Sunday Akintoye
Claudia Dumitrescu
Todd Theman
Elizabeth Hart
Azar Khosravi
Carolee Cutler
Penny Andreopoulou
William Chong
Diala El-Maouche

FD Collaborators

Penny Feuillan	Shlomo Wientroub
Paolo Bianco	Harvey Kushner
Arabella Leet	Ed FitzGibbon
John Butman	Tom Shawker
Janice Lee	Francesco Celi
Clara Chen	Scott Paul
James Reynolds	Jeff Kim
Chris Austin	Jim Inglese
Wei Zheng	Catherine Chen
John Northup	