CME Series on Lysosomal Disorders

Skeletal Involvement in Lysosomal Disorders

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Dr. Goker-Alpan is on the Advisory Board/Consultant for Chiesi, Takeda, Sanofi, Prevail/Lilly, Sparks Therapeutics, Uniqure, Exegenesis, Astellas, Freeline, Team Sanfilippo. She receives grants/research support from Chiesi, Sanofi, Takeda, Prevail/Lilly, Spark Therapeutics, Amicus, Freeline, Sangamo, Cyclo, Odorsia, $DMT, Homology, Protaliz. She is on the speaker bureau for Sanofi, Takeda, Amicus, Chiesi

Dr. Kamath is on the Advisory Board for Spur Therapeutics and Intrinsic Therapeutics. He is also a consultant for Sanofi and Takeda.

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This activity has been supported by educational grants from Takeda and Ultragenyx.

Lysosomal Disorders Presenting As Primary Skeletal Disease

Mucopolysaccharidoses (MPS)

- MPS I (Hurler, Hurler-Scheie, Scheie): Dysostosis multiplex, spinal deformities
- MPS II (Hunter): Joint stiffness, skeletal dysplasia
- MPS IV (Morquio): Severe skeletal abnormalities, odontoid hypoplasia
- MPS VI (Maroteaux-Lamy): Bone deformities, joint contractures

Other LSDs

- Gaucher Disease: Bone marrow infiltration, osteonecrosis, fractures
- Multiple Sulfatase Deficiency: Dysostosis multiplex, short stature
- Mucolipidosis II/III: Severe skeletal dysplasia, joint immobility

Suggested Mechanisms of Skeletal Involvement in Lysosomal Disorders

Molecular Pathophysiology

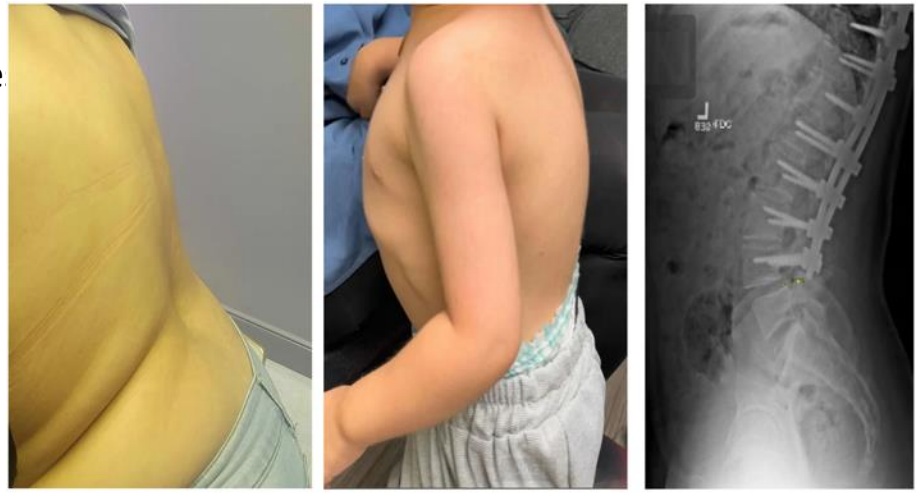
- Accumulated substrate(s) : Glycosaminoglycans (GAGs) or sphingolipids lipids in lysosome
- Disrupted chondrocyte and osteoblast function, impairing extracellular matrix (ECM) synthesis
- Upregulated inflammatory cytokines (e.g., TNF-α, IL-1β), promoting osteoclastogenesis

Cellular Effects

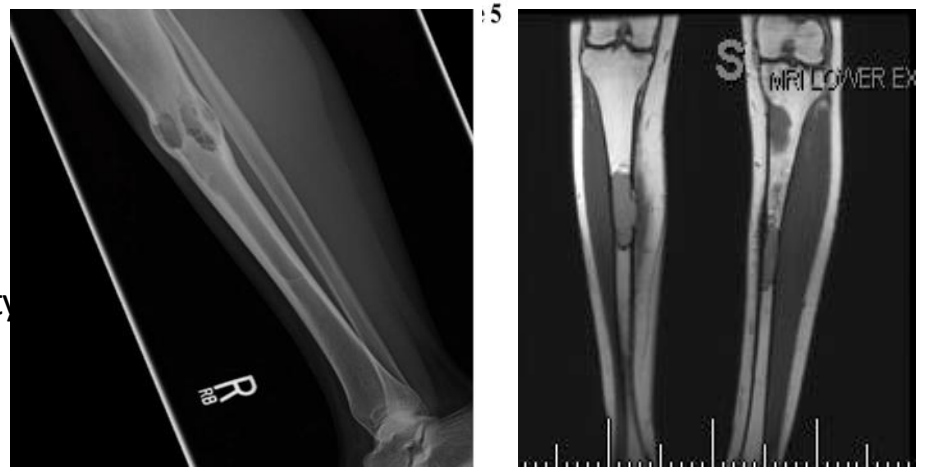
- Altered endochondral ossification causes dysostosis multiplex (e.g., flattened vertebrae, abnormal phalanges)
- GAG deposition in synovium and cartilage induces joint stiffness and contractures
- In Gaucher disease, glucocerebroside accumulation in macrophages causes bone marrow infiltration

Bone Remodeling Imbalance

- Increased receptor activator of NF-κB ligand (RANKL) signaling enhances osteoclast activity
- Reduced osteoprotegerin (OPG) levels exacerbate bone resorption, causing osteopenia
- Impaired bone marrow-adipose tissue interaction



Goker-Alpan, JIMD, 2024



Presenter's own images

Interdisciplinary Approach

Multidisciplinary Approach

- Integrates geneticists or metabolic specialists, physical therapists, orthopedic surgeons, anesthesiologist
- Coordinates diagnostics, therapeutic interventions, and long-term monitoring

Team Care Benefits

- Holistically manages skeletal and systemic manifestations
- Improves functional outcomes and quality of life

Key Responsibilities

- Regular imaging (X-ray, MRI) to monitor skeletal progression
- Individualized treatment plans based on disease severity
- Patient and family education for adherence to therapies

Orthopedic Surgeon's Role

- Assesses skeletal deformities (e.g., kyphoscoliosis, hip dysplasia) via imaging
- Performs corrective procedures (e.g., spinal fusion, osteotomy, joint realignment)
- Collaborates with team

Prognosis

- Early surgical and medical intervention mitigates skeletal damage
- Team care ensures comprehensive, long-term management
- for pre/post-surgical optimization

Supportive Care

- Orthotics, physical therapy, pain management

Bone Complications in Lysosomal Storage Disorders

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Disclosures

- Consulting fees, honoraria
  - Sanofi
  - Shire/Takeda
  - Spur Therapeutics

Outline

- Introduction to lysosomal storage disorders (LSDs)
- Imaging of skeletal abnormalities in LSDs
  - MPS (dysostosis multiplex)
  - Pyknodysostosis
  - Gaucher disease
- Management of bone abnormalities in LSDs
  - Role of the orthopedic surgeon
- Recent developments
- Q&A

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Lysosomal Storage Disorders

- Individually rare, but as a group affect ~1:5000 live births
- Accumulation of glycosaminoglycans in the lysosomes
- Usually caused by genetic mutation resulting in failure to manufacture or process enzyme needed for its breakdown
- This can affect the skeleton by causing accumulation of substrates in macrophages or connective tissue cells
- The most common of these are Gaucher disease and the mucopolysaccharidoses (MPSs)
- Pathophysiology likely involves a combination of space occupation, inflammation, and epigenetic factors

Lysosomal Storage Disorders

Lysosomal storage disorders with a skeletal phenotype.

	Type	Enzyme	Gene(s)	Main clinical findings
3	Gaucher disease	β-glucocerebrosidase	GBA1	Avascular necrosis, bone crises Osteoporosis, fractures Hepatosplenomegaly Cytopenia Neurologic
	Mucopolysaccharidoses	Table 3	Table 3	Dysostosis, coarse facies, short stature, arthropathy coarse facies, visceromegaly, cataracts, psychomotor retardation
	α-Mannosidosis	α-mannosidase	*MANB*	Dysostosis, coarse facies, visceromegaly, cataracts, psychomotor retardation
	Fucosidosis	α-fucosidase	*FUCA1*	Dysostosis, coarse facies, angiokeratoma, psychomotor retardation
1	Sialidosis I/II	α-neuraminidase	*NEU1*	Dysostosis, coarse facies, seizures, cherry red spot, viceromegaly, corneal clouding, psychomotor retardation
	Galactosialidosis	Cathepsin-A	*PPCA*	Dysostosis, coarse facies, psychomotor retardation, viceromegaly, corneal clouding, angiokeratoma
	Mucolipidosis II/III (I-Cell disease/ pseudo-Hurler polydystrophy	UDP-N-acetylglucosamine: lysosomal enzyme N-acetylglucosamine-1-phosphotransferase	*GNPTAB* *GNPTG*	Similar to MPS I
	Multiple sulfatase	Sulfatase modifying factor 1	*SUMF1*	Similar to MPS II
2	Pycnodysostosis	Cathepsin K	*CTSK*	Short stature, hypoplasia of the mandible, skull abnormalities pathologic fractures

From Clarke *et al*, *Best Practice Res Clin Endocrin Metab.* 2015; 29: 219-235.

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Mucopolysaccharidoses (MPSs)

- Group of 11 LSDs caused by defects in catabolism of glycosaminoglycans

The mucopolysaccharidoses.

Type	Syndrome	Enzyme	Gene	Primary storage material
MPS I	Hurler, Hurler-Scheie Scheie	α-L-iduronidase	*IDUA*	Heparan sulfate + Dermatan sulfate
MPS II	Hunter	Iduronate-2-sulfatase	*IDS*	Heparan sulfate + Dermatan sulfate
MPS III	Sanfilippo A Sanfilippo B Sanfilippo C Sanfilippo D	Heparan N-sulfatase α-N-acetyl glucosaminidase Acetyl-CoA:α-glucosaminide acetyltransferase N-acetylglucosamine 6-sulfatase	*SGSH* *NAGLU* *HGSNAT* *GNS*	Heparan sulfate
MPS IV	Morquio A Morquio B	N-acetylgalactosamine-6- sulfatase β-D-galactosidase	*GALNS* *GLB1*	Keratan sulfate+ Chondroitin-6-sulfate Keratan sulfate
MPS VI	Maroteaux-Lamy	N-acetylgalactosamine-4-sulfatase	*ARSB*	Dermatan sulfate
MPS VII	Sly	β-glucuronidase	*GUSB*	Heparan sulfate + Dermatan sulfate + Chondroitin-4, -6 sulfates
MPS IX	–	Hyaluronidase	*HAL1*	Hyaluronan

From Clarke *et al*, *Best Practice Res Clin Endocrin Metab* 2015; 29: 219-235.

Mucopolysaccharidoses (MPSs)

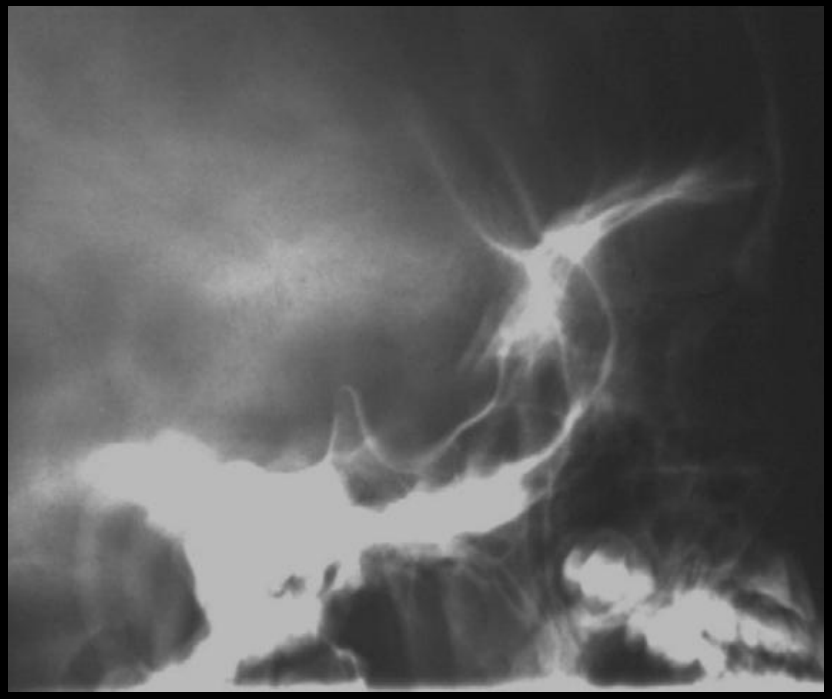
- Each MPS is a progressive multisystem disorder with skeletal manifestations a major cause of morbidity
- Although the primary enzyme deficiency and accumulated substrate have been identified for each MPS, the mechanism underlying the disease symptoms and skeletal manifestations is not clear, and presentation is very heterogeneous
- Skeletal disorders are the presenting symptom for most MPS types, with exception of MPS III (Sanfilippo)
- Skeletal findings (dysostosis multiplex) result from defective endochondral and membranous ossification and bone maturation

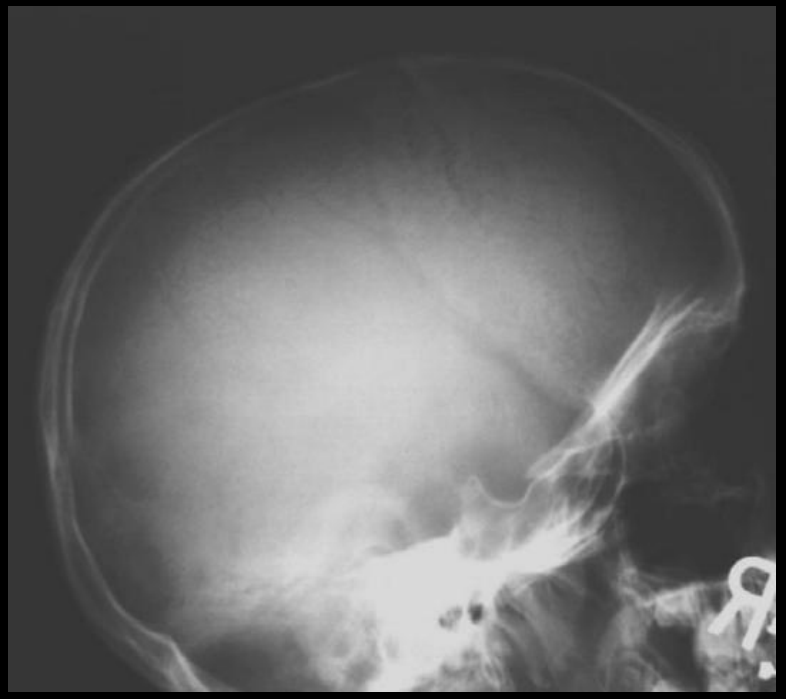
Dysostosis Multiplex

- Variable constellation of skeletal abnormalities and changes in bone growth and development
- All types of MPS show dysostosis multiplex to varying degrees
- Dysostosis multiplex is also a feature of mucolipidoses and other lysosomal storage diseases, including
  - Mucolipidoses (ML): Sialidosis I/II, ML II (I-Cell disease), ML III (Pseudo-Hurler polydystrophy), ML IV
  - Other storage diseases: α-Mannosidosis, Fucosidosis, Galactosialidosis, Multiple sulfatase deficiency, Carbohydrate-deficient glycoprotein syndrome, GM I gangliosidosis, Geleophysic dysplasia

Imaging of Dysostosis Multiplex

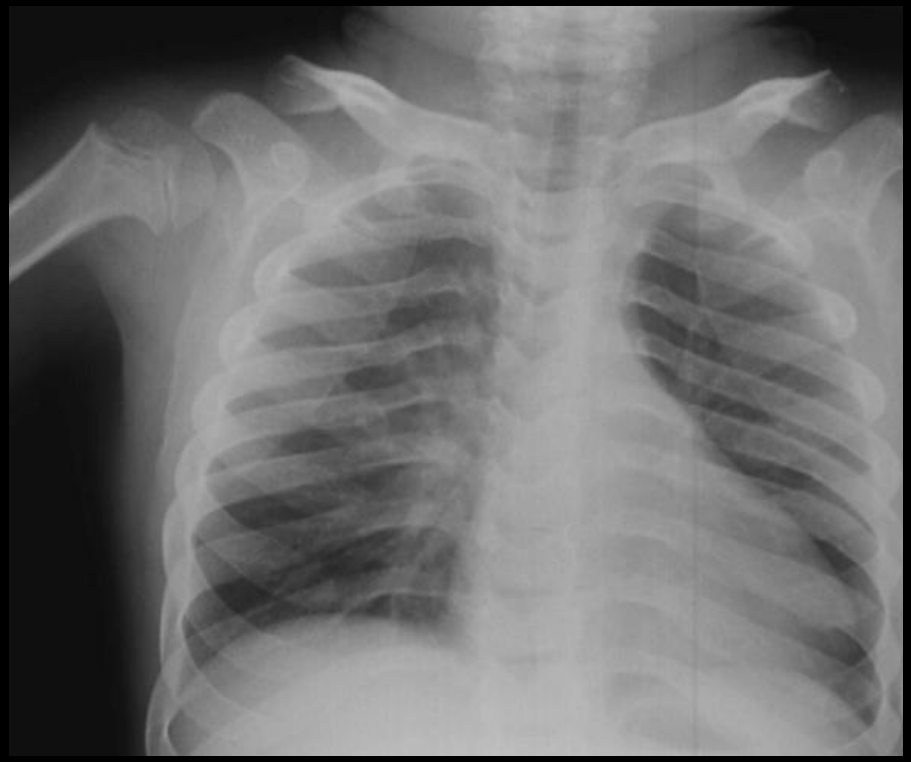
- Skull: macrocephaly, J-shaped sella turcica, thickened calvarium

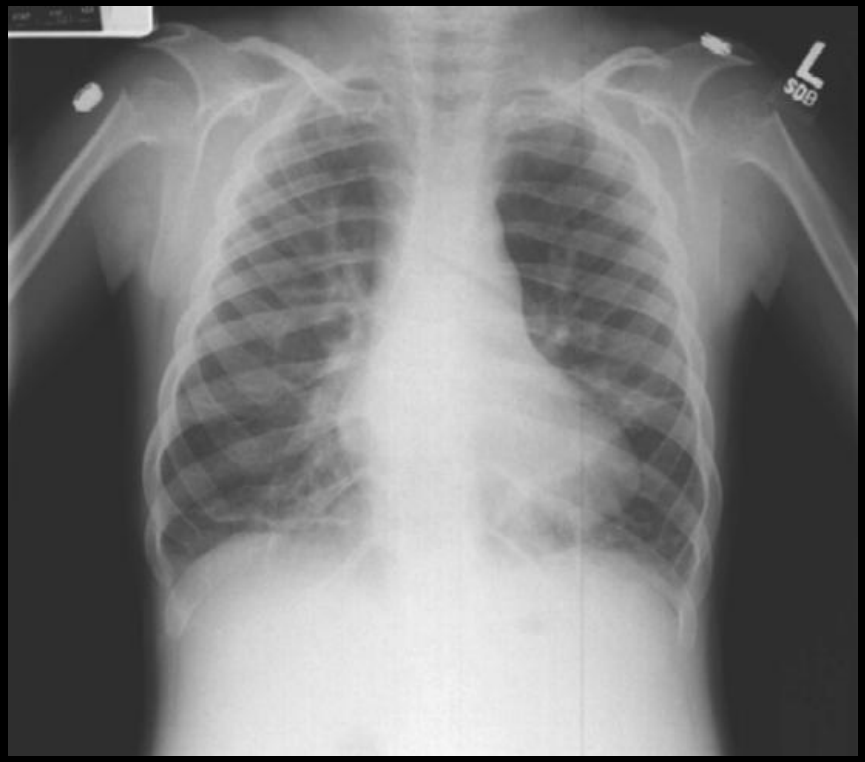




Imaging of Dysostosis Multiplex

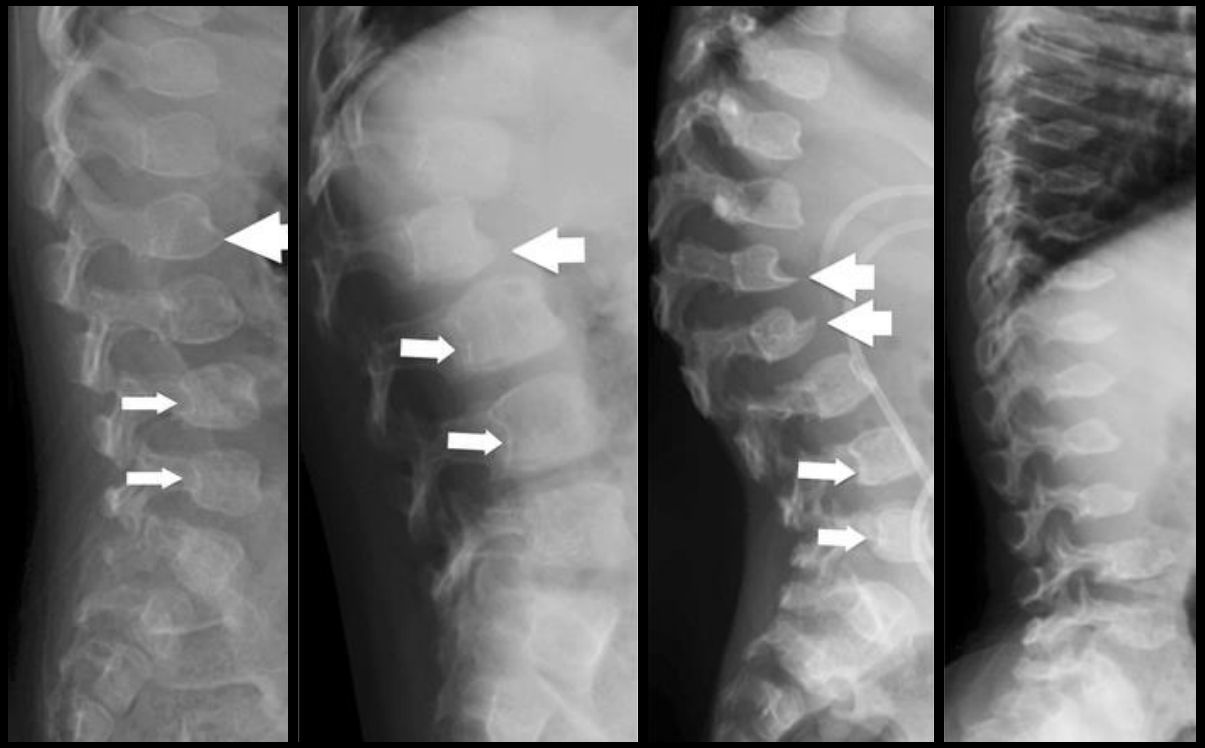
- Thorax: short/thick clavicles, paddle/oar-shaped ribs, short sternum (proximal humeri show medial humeral notching)





Imaging of Dysostosis Multiplex

- Spine: platyspondyly with beaked/notched vertebral bodies, posterior scalloping, odontoid dysplasia



From Nicolas-Jilwan and Al-Sayed, *Pediatric Radiology* 2018; 48: 1503-1520.

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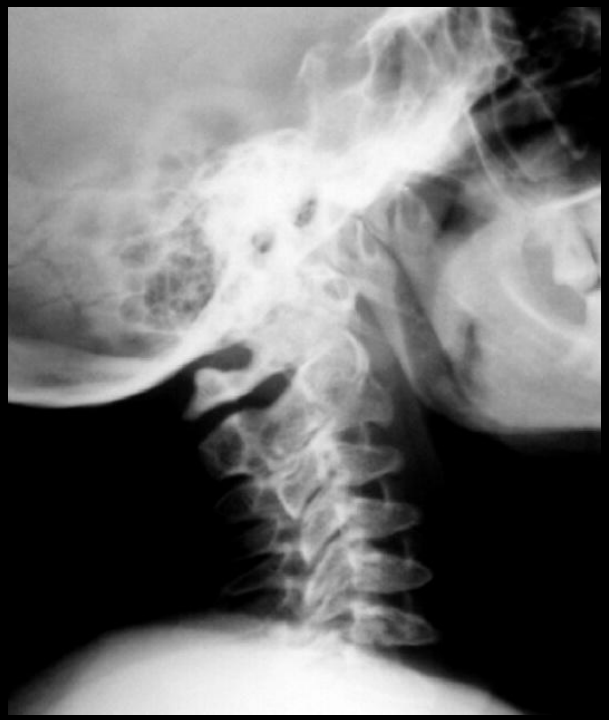
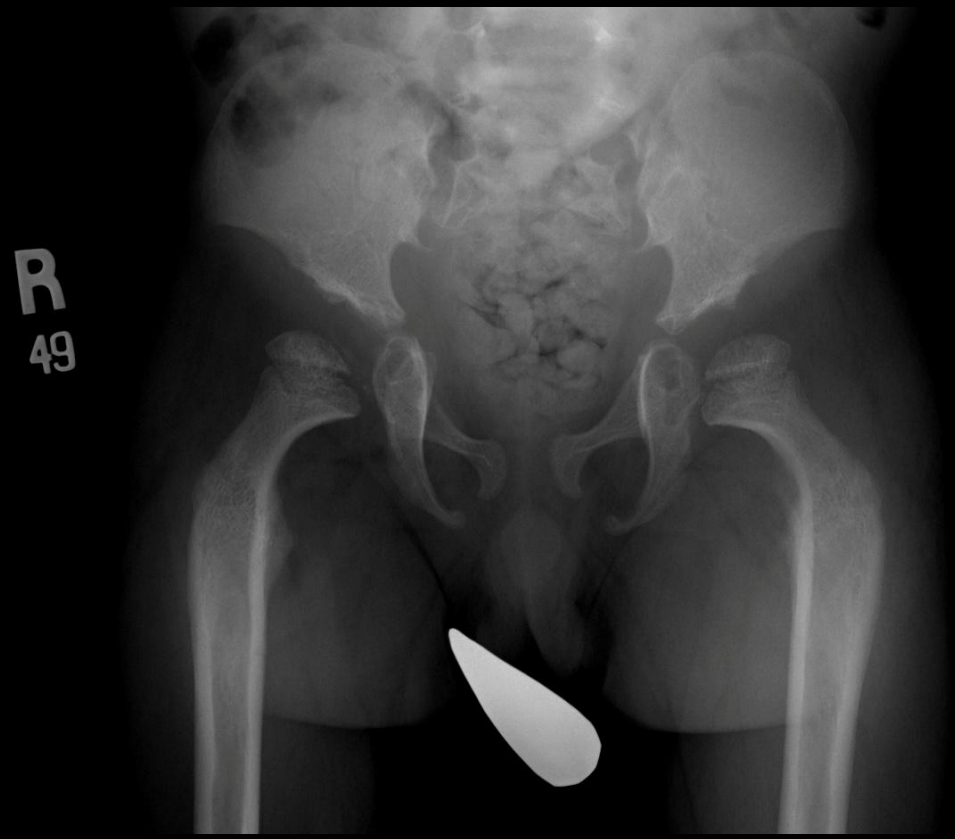


From Di Cesare *et al*, *Case Reports Med* 2012; 2012: 324596.

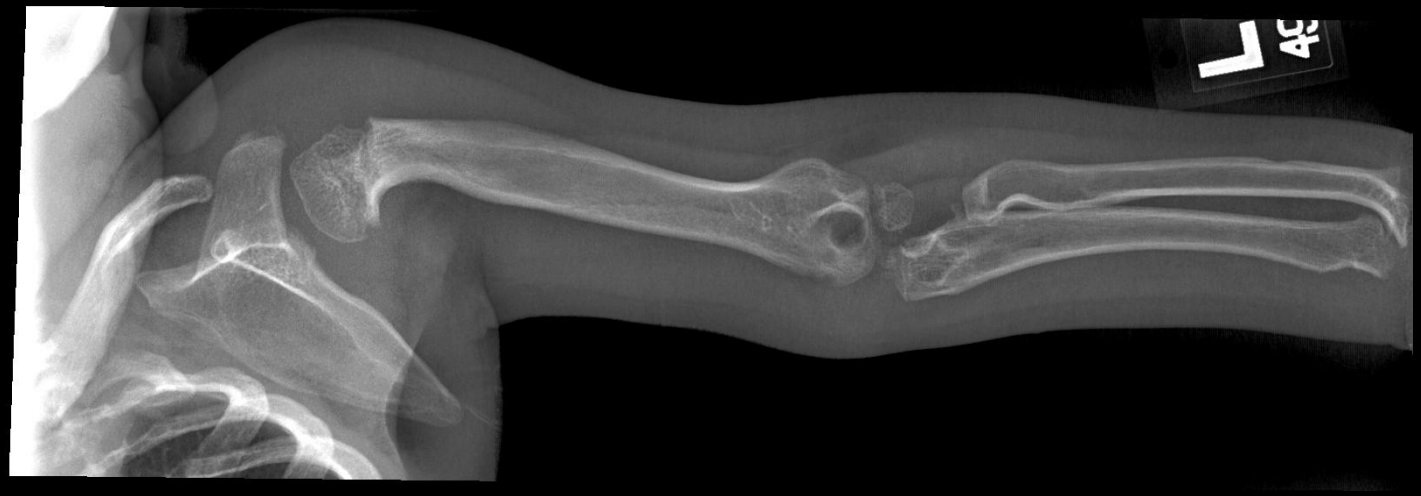
Imaging of Dysostosis Multiplex

- Pelvis: rounded iliac wings, tapered iliac bones (proximal femurs show dysplastic epiphyses and long femoral necks)



Imaging of Dysostosis Multiplex

- Long bones: hypoplastic/fragmented epiphyses, short/thick diaphyses (long/narrow femoral necks, proximal humeral notching)



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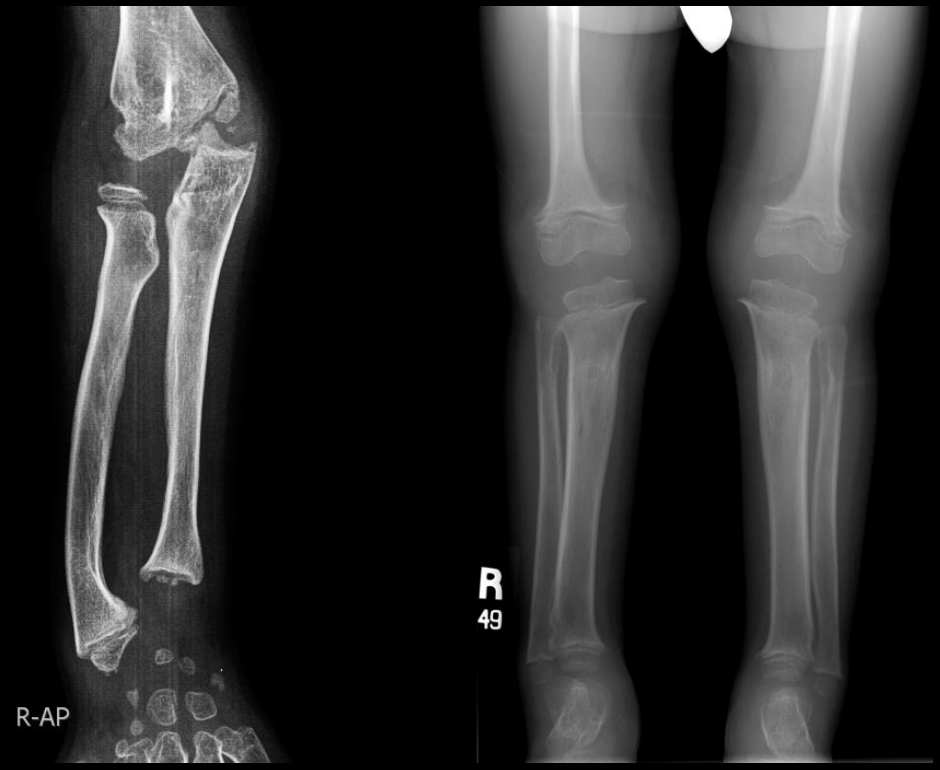
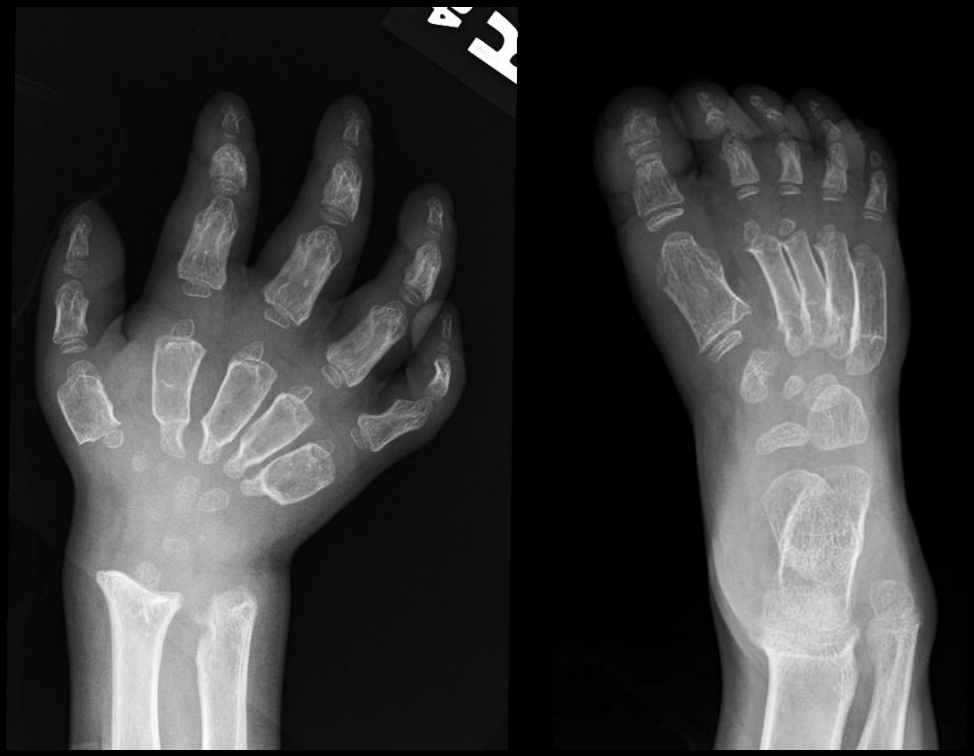


Imaging of Dysostosis Multiplex

- Hands/feet: short/thick metacarpals and metatarsals with proximal pointing, irregular hypoplastic carpal/tarsal bones



Skeletal Complications in MPS

- Disturbance in linear bone growth leading to short stature (typically starts 18 mo, little growth after 8 y)
- Morphologic bone abnormalities:
  - Macrocephaly
  - Spinal deformity with kyphoscoliosis, gibbus, and odontoid dyplasia, plus dural and ligament thickening, which can cause cord compression
  - Chest deformity with pectus carinatum and rib deformities, which can cause restrictive lung disease
  - Progressive arthropathy with contractures and joint destruction

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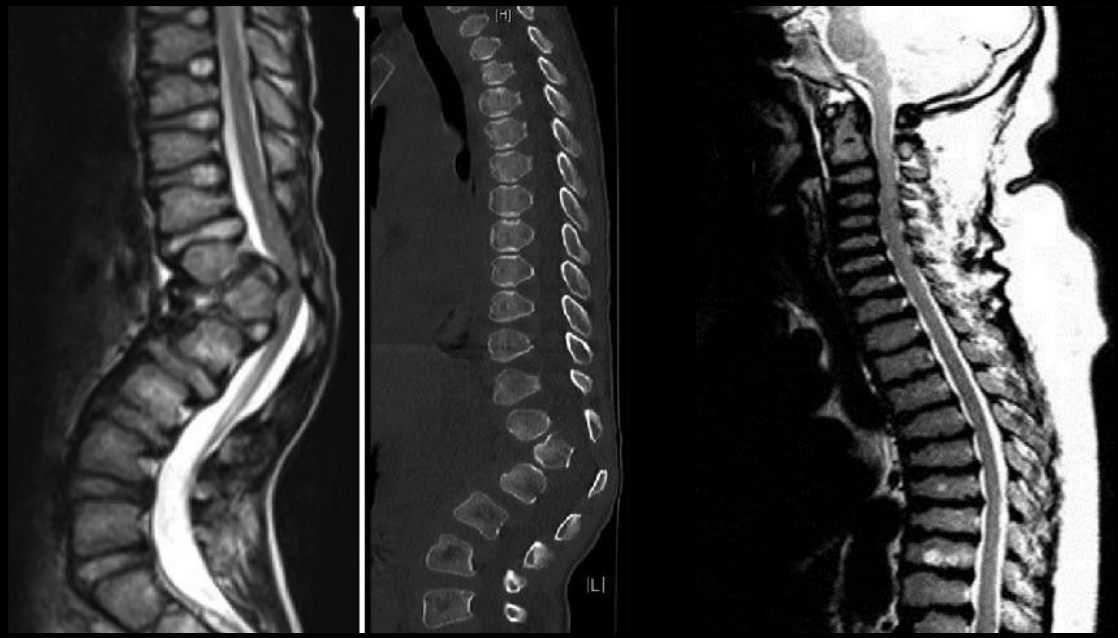

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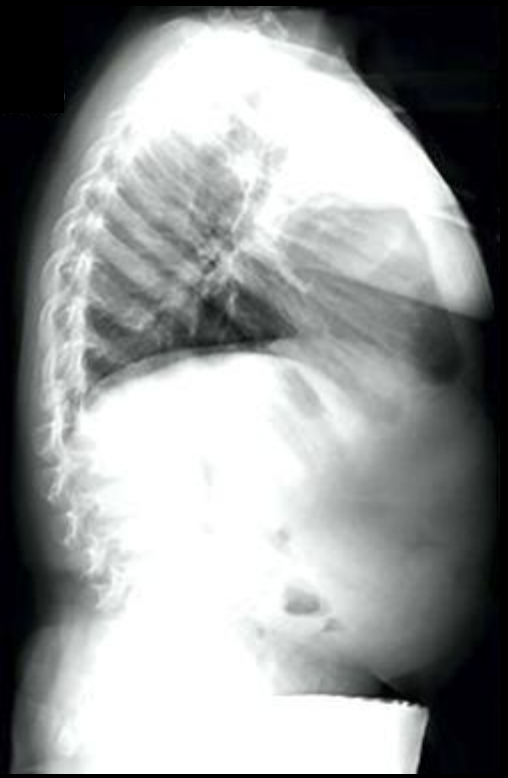

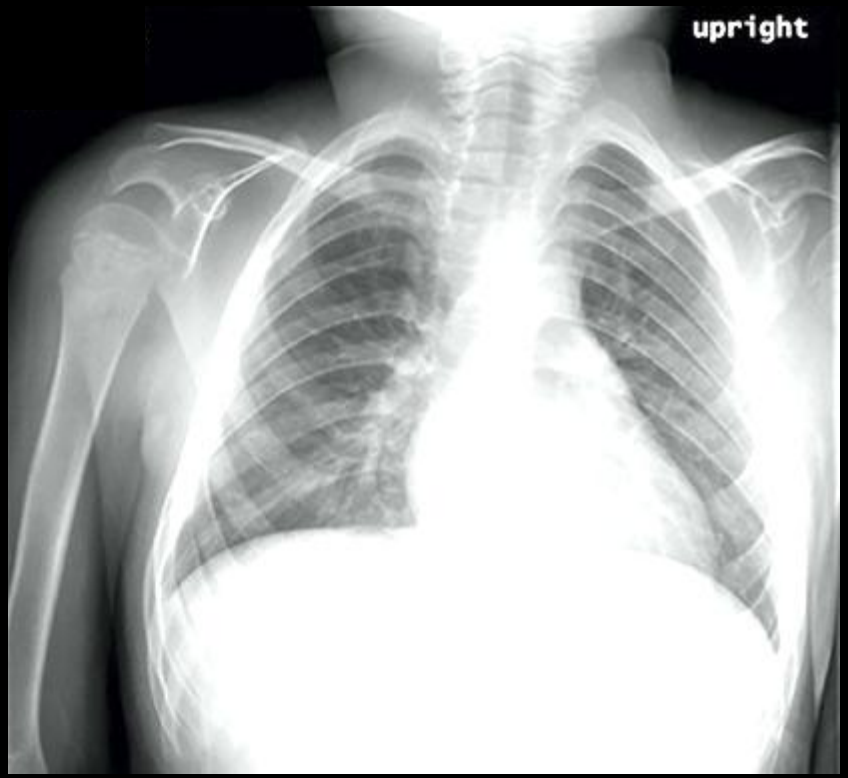

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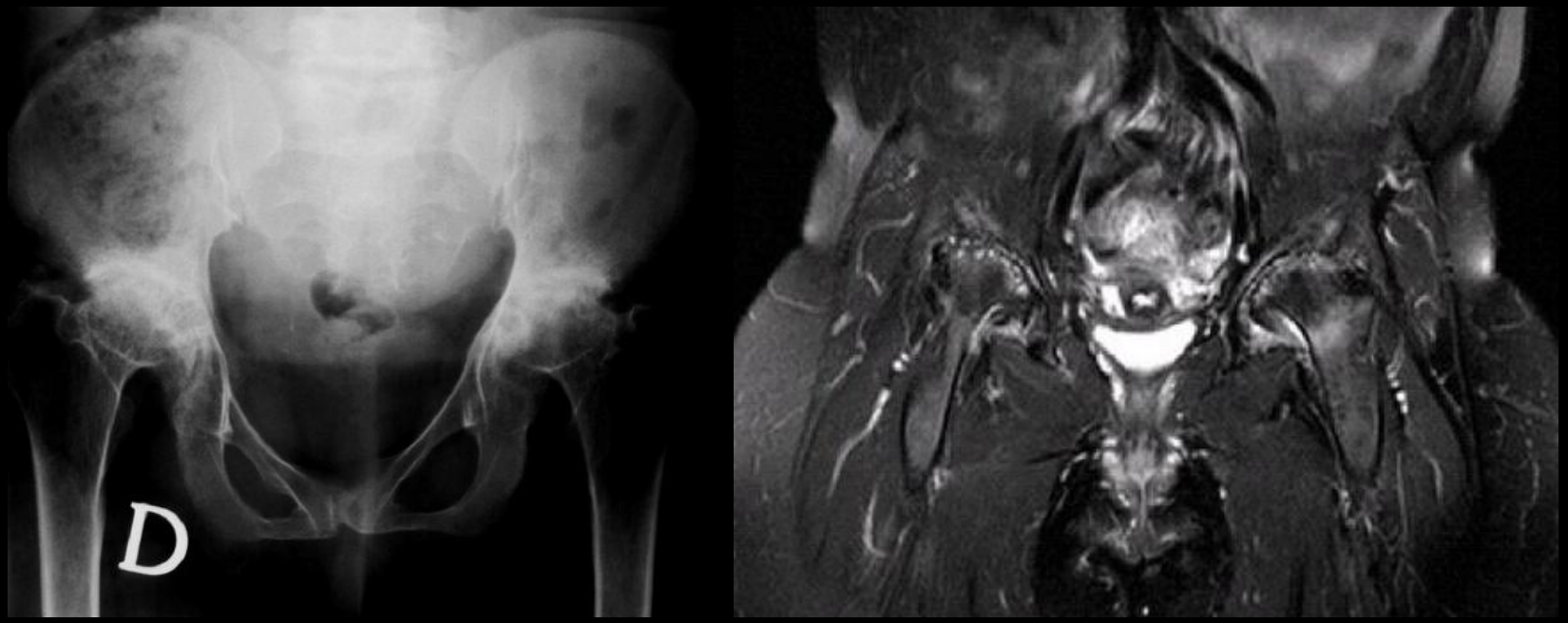

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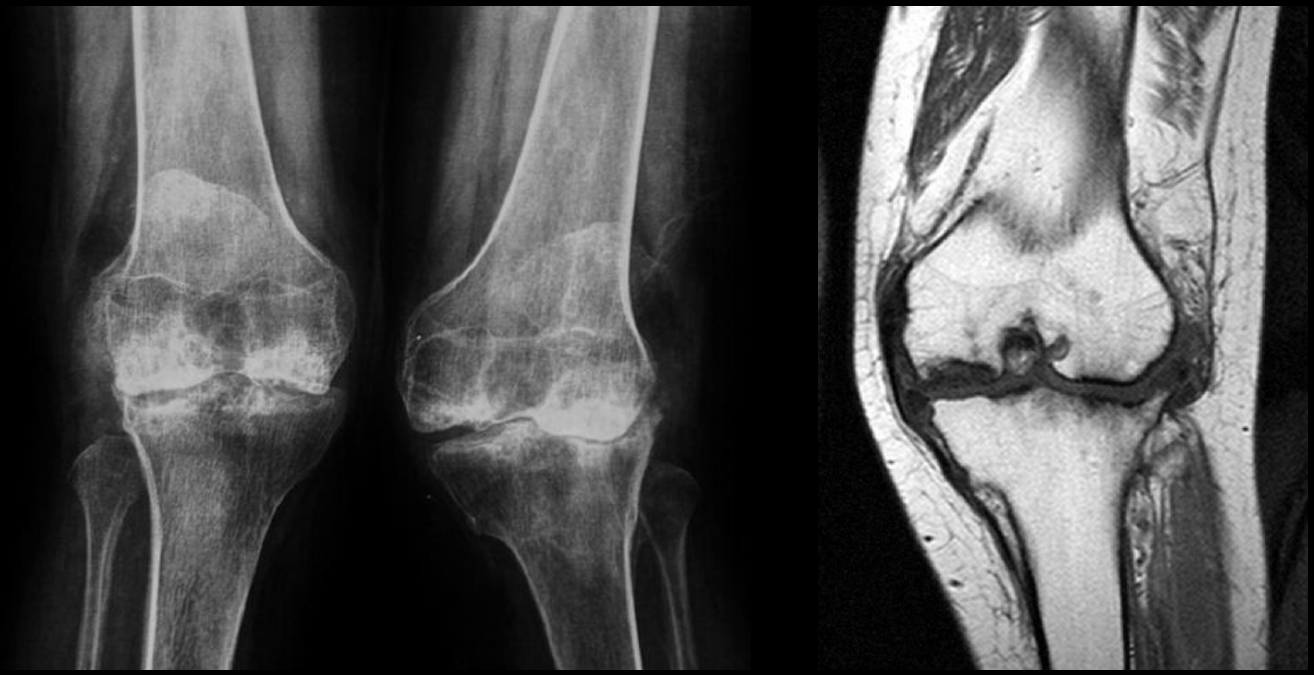

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Pyknodysostosis

- Rare autosomal recessive bone dysplasia caused by deficiency of cathepsin K, which is necessary for osteoclast function
- Clinical features:
  - Short stature, especially limbs
  - Diffuse increased bone density
  - Delayed closure of cranial sutures
  - Frontal and occipital bossing
  - Short, broad hands and nail hypoplasia
  - Long bone fractures with minimal trauma

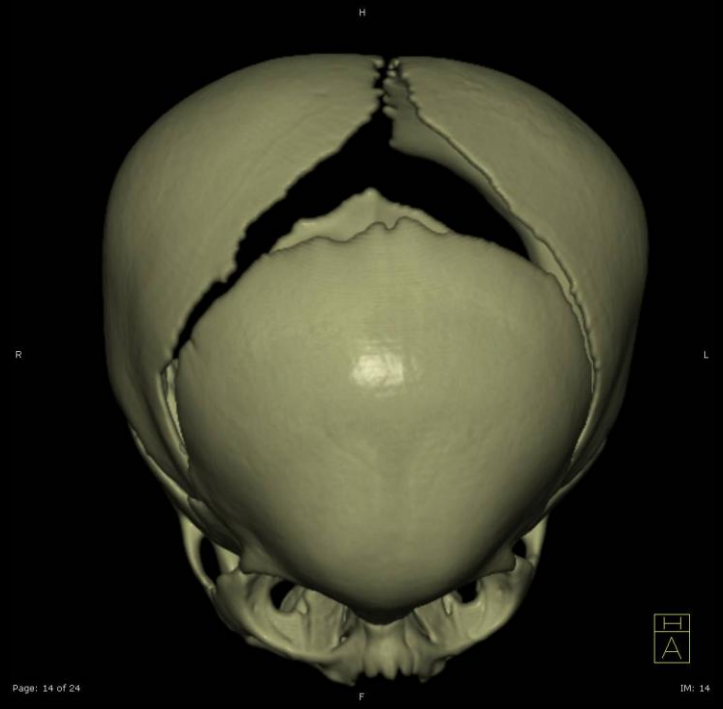
Imaging of Pyknodysostosis

- General: short stature (Toulouse-Lautrec)

From Paul Sescau, 1894. Musée Toulouse-Lautrec, Albi.

Imaging of Pyknodysostosis

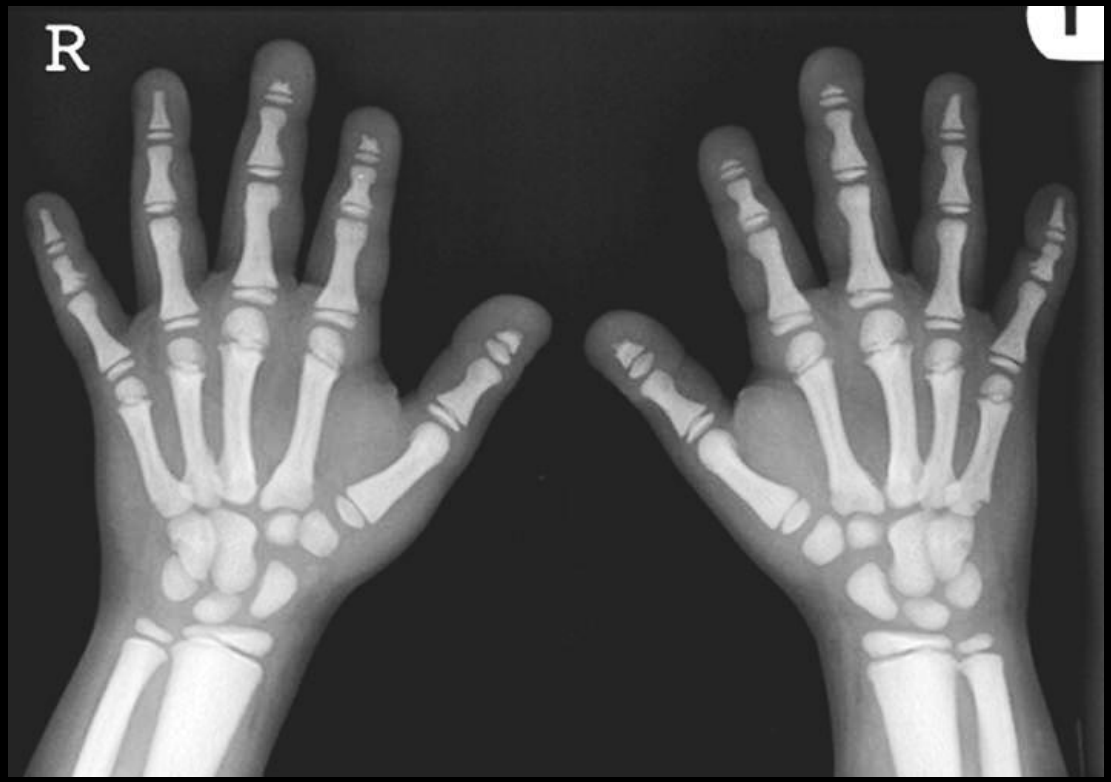
- Head: marked delay in suture closure, frontoparietal bossing, calvarial thickening



From Andrew Dixon, Radiopaedia.org, rID: 10291.

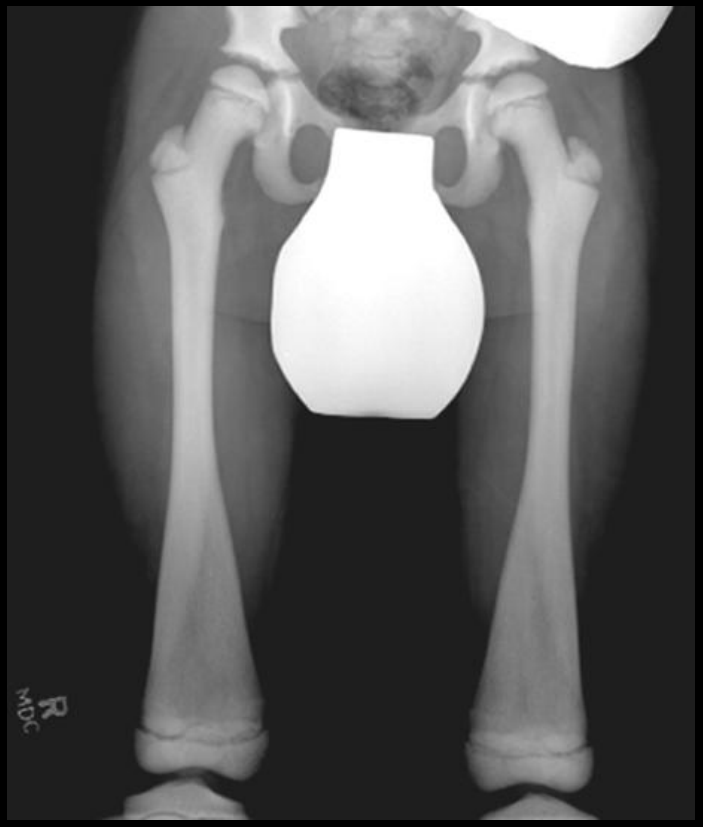
Imaging of Pyknodysostosis

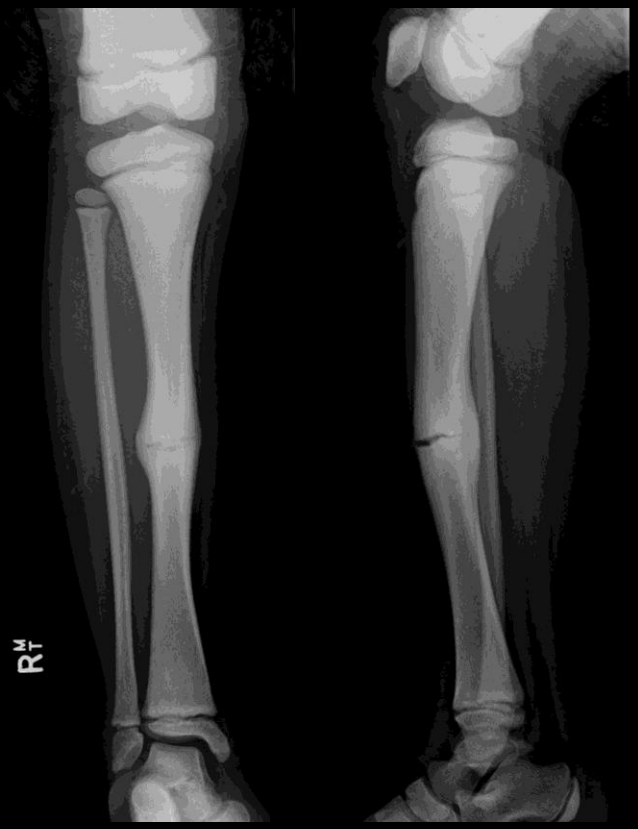
- Hands: short, stubby fingers with partial agenesis of distal phalanges, delayed bone age



Imaging of Pyknodysostosis

- Long bones: generalized osteosclerosis with narrowed medullary cavity, fractures





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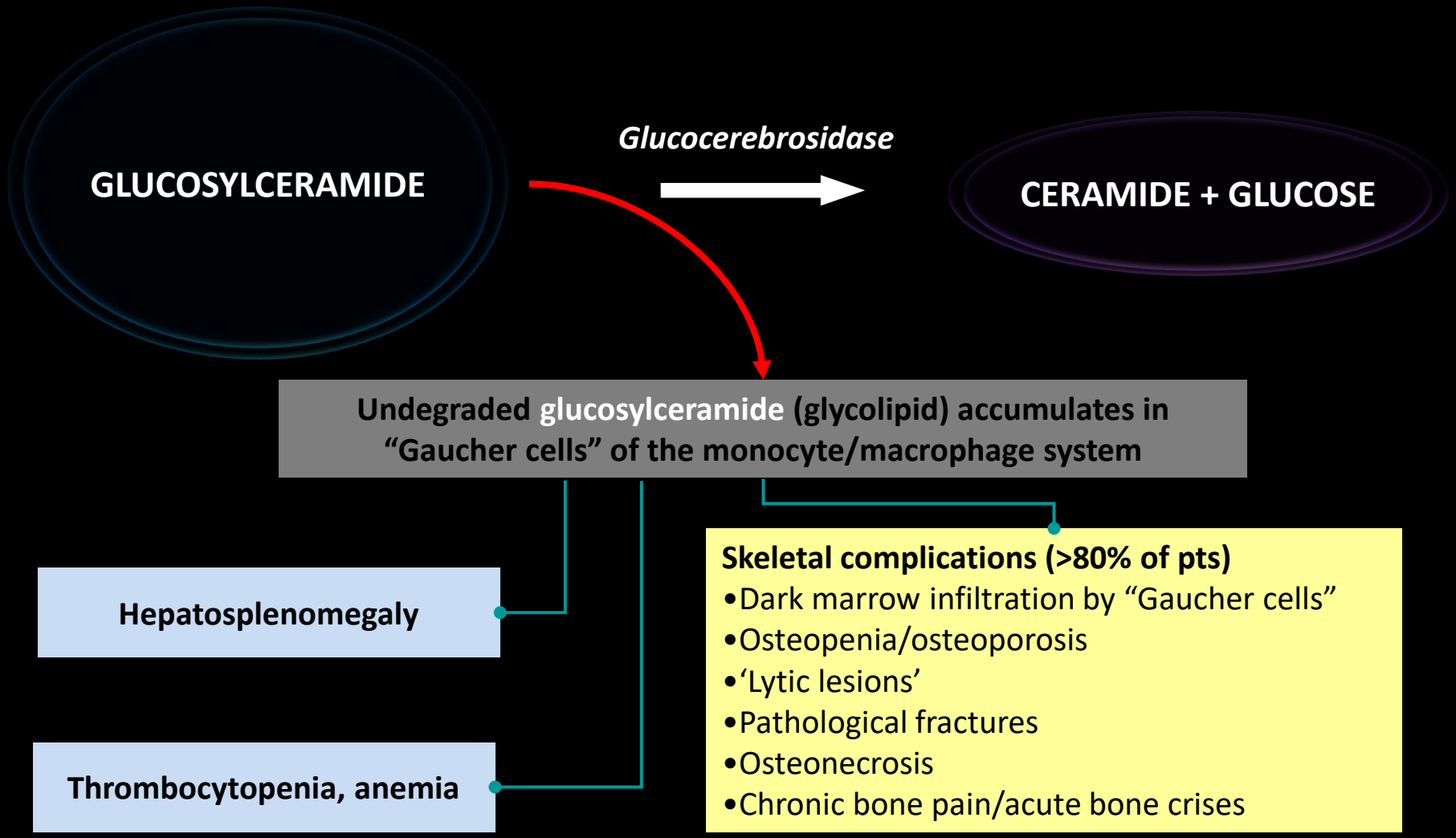
Gaucher Disease

- Best studied/understood lysosomal storage disorder
- Autosomal-recessive deficiency of acid β-glucocerebrosidase
- Almost 200 known gene mutations, but most common mutation (N370S) accounts for ~50% of cases
- Prevalence is 1:40,000 to 1:60,000
- 3 types: Type 1 (non-neuronopathic) is most common

Gaucher Disease



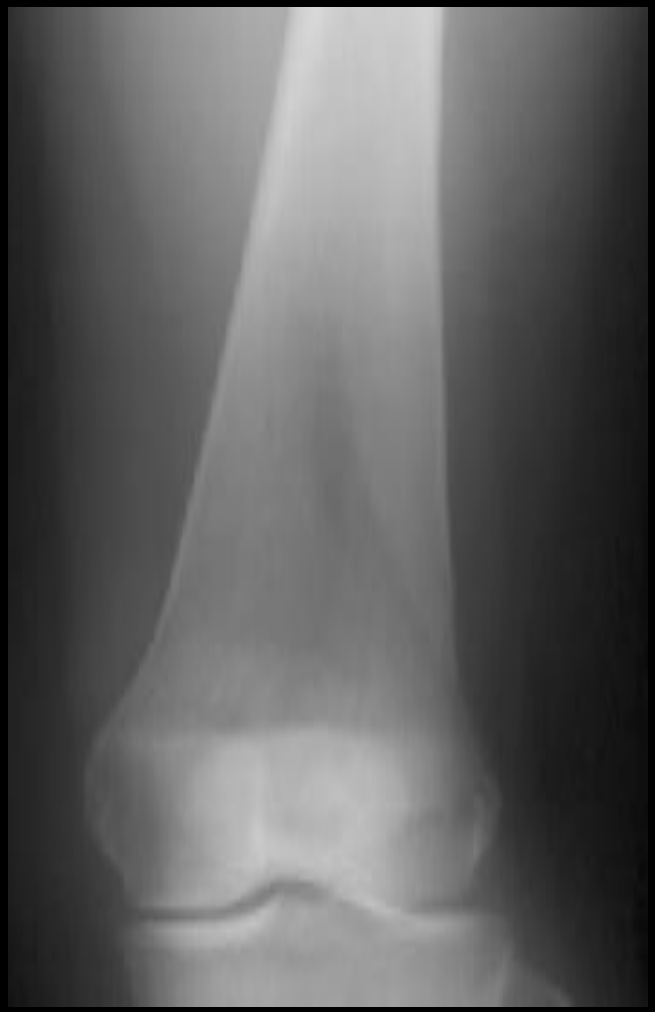
Gaucher Disease

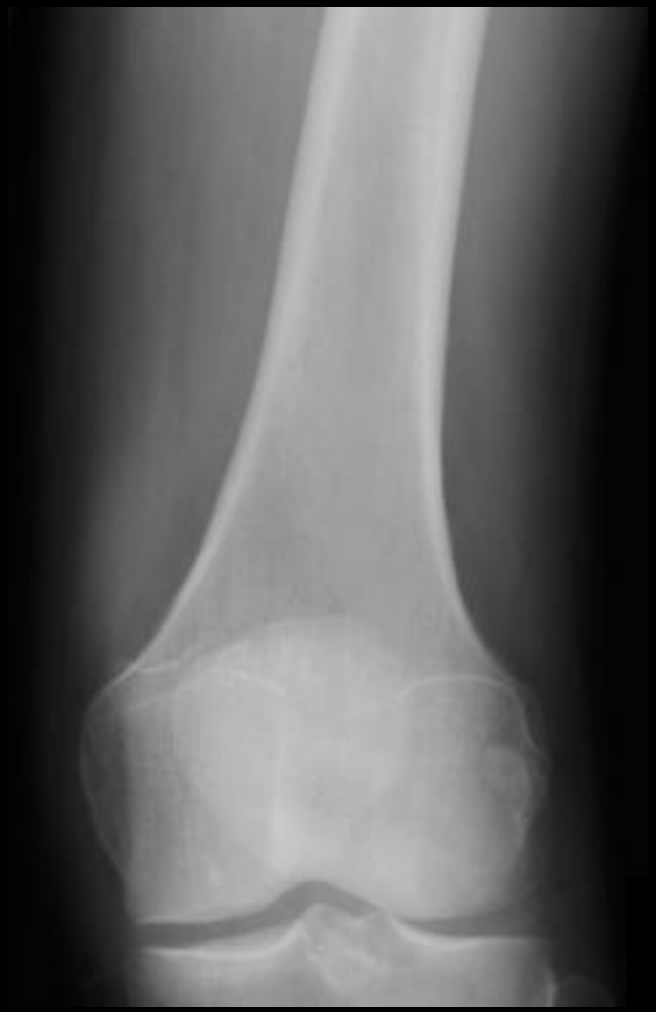
- Deficient activity of glucocerebrosidase during development:
  - **Slowed growth (75% without rx)**
  - **Delayed puberty (60% without rx)**
  - Splenomegaly and hepatomegaly (>80% at time of dx)
  - Thrombocytopenia and anemia (40% at time of dx)
  - **BONE DISEASE (>80% at time of dx)**

    Varied skeletal complications

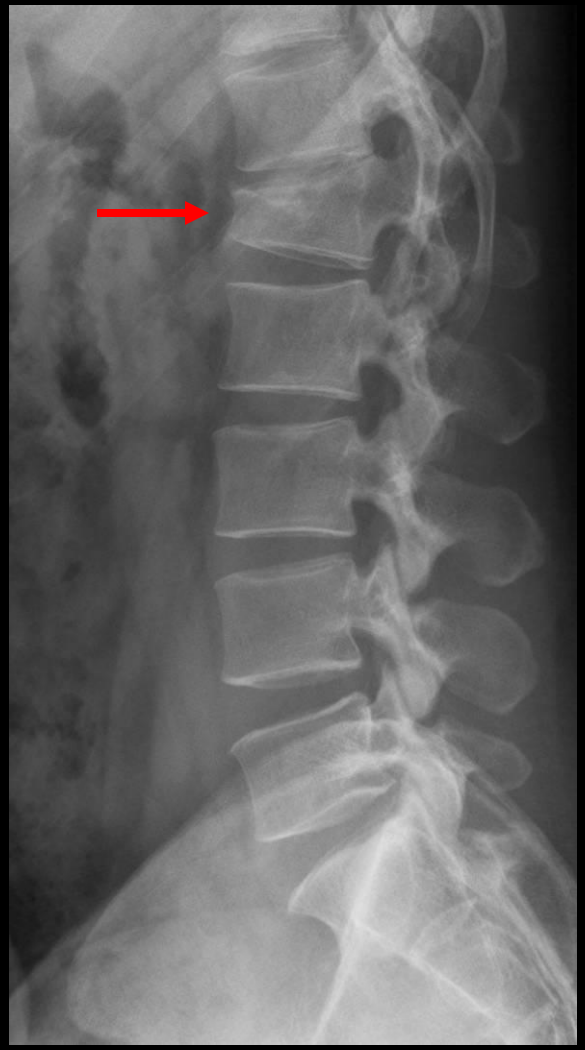
From Kaplan *et al.*, *Eur J Pediatr.* 2013; 172: 447-458.

X-Ray: Erlenmeyer Flask Deformity

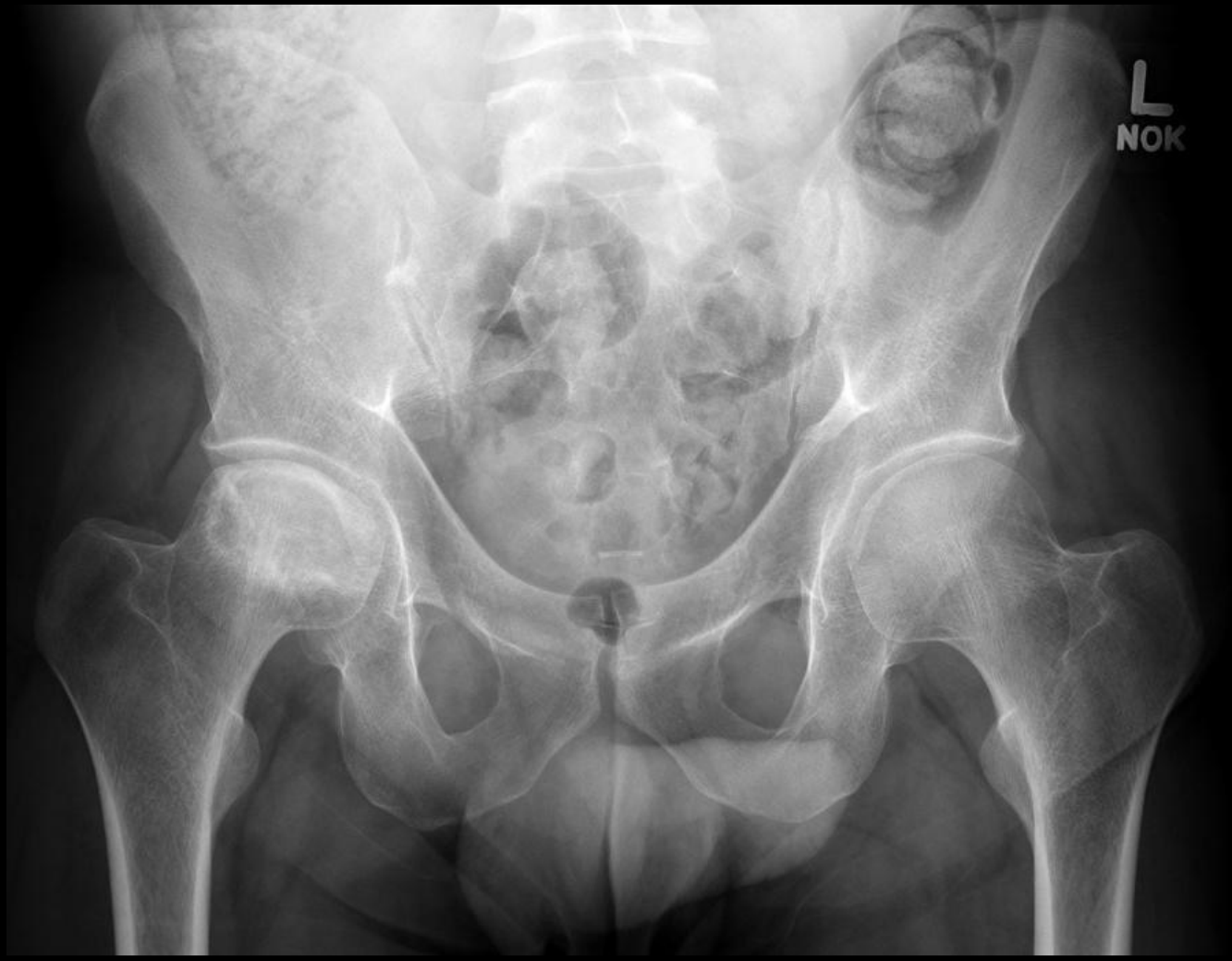




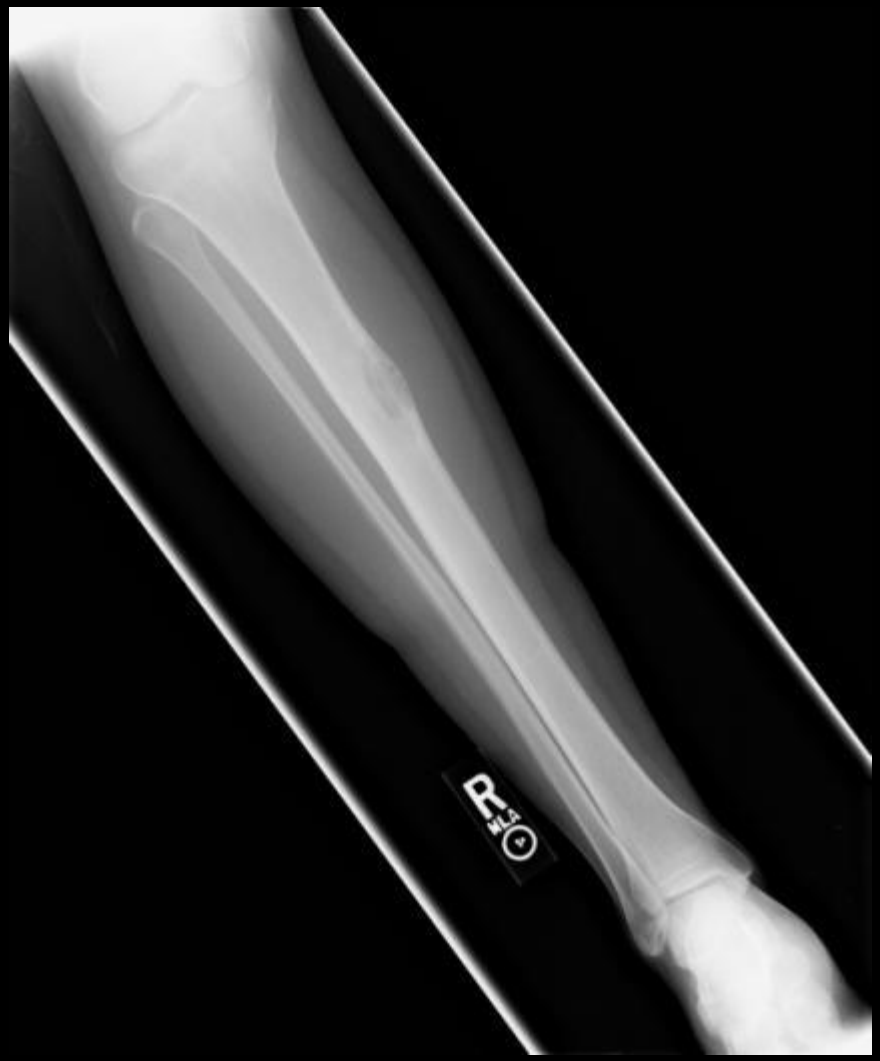
X-Ray: Fracture



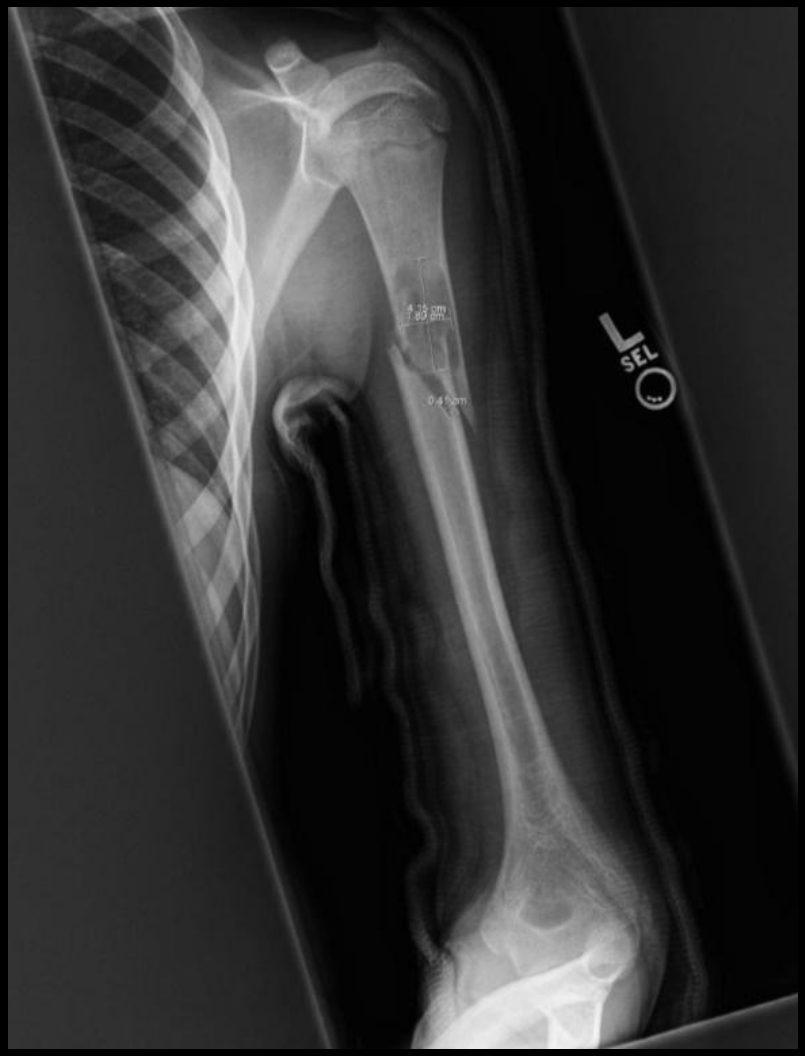
X-Ray: Osteonecrosis



X-Ray: Lytic Lesion



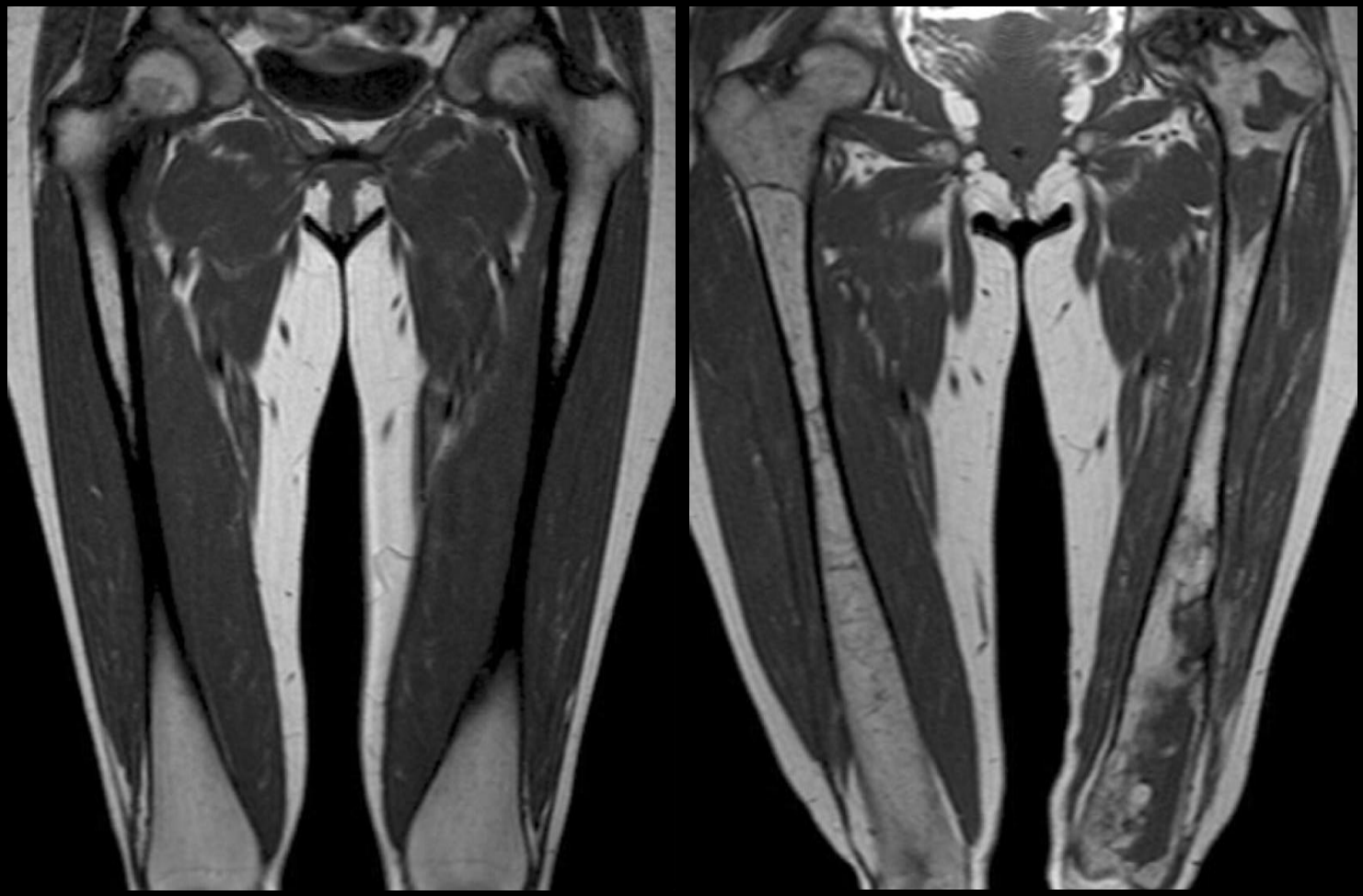
X-Ray: Pathologic Fracture



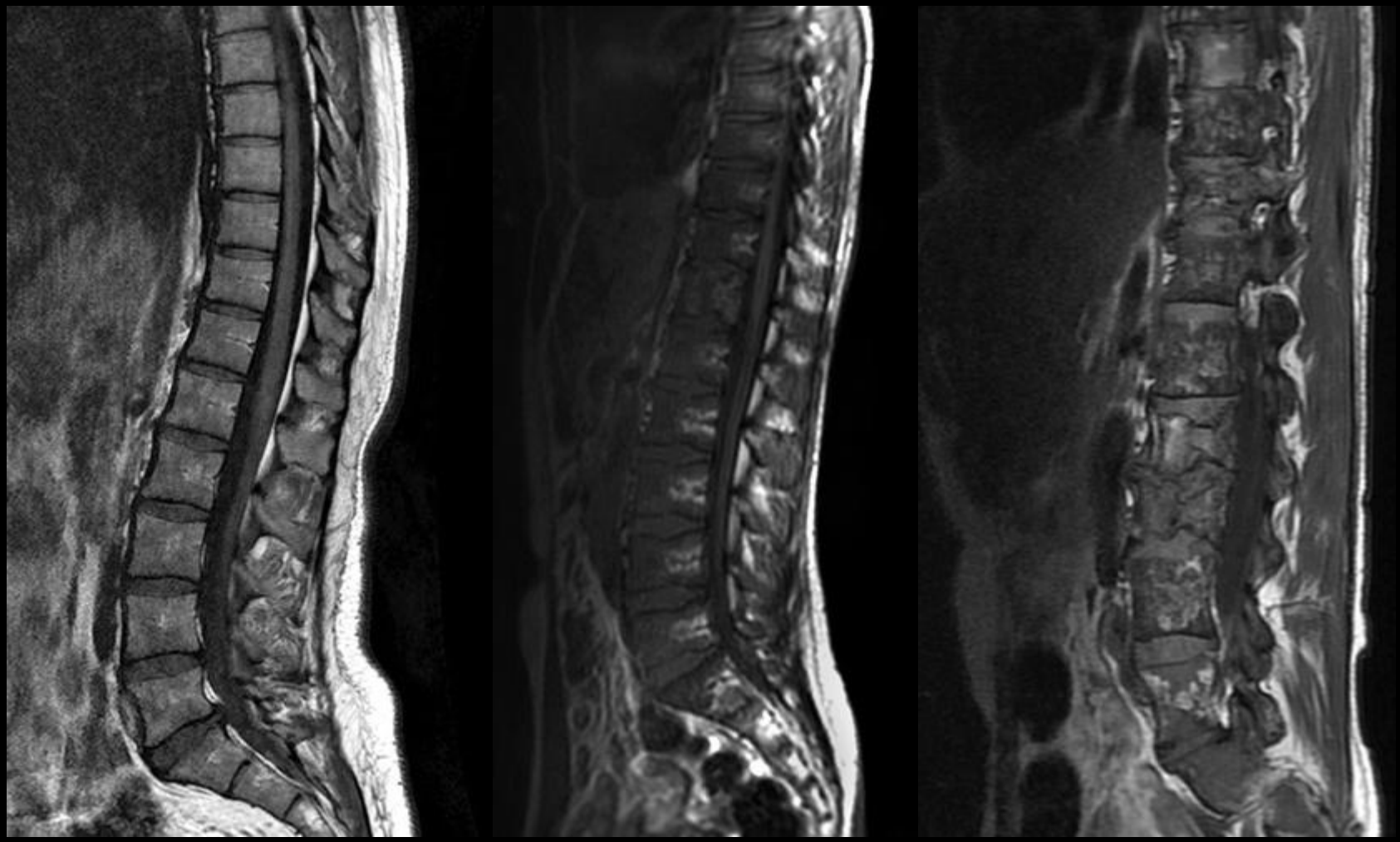
MRI in Gaucher Disease

- On MRI, marrow infiltrated with Gaucher cells typically appears hypointense (dark) on both T1- and T2-weighted images (‘dark marrow’)
- Affected marrow can also be T2 hyperintense, which can be also be seen with superimposed osteonecrosis, marrow infarction, or infection
- Focal bone lesions (‘lytic lesions’ or ‘Gaucheromas’) may be seen in some patients

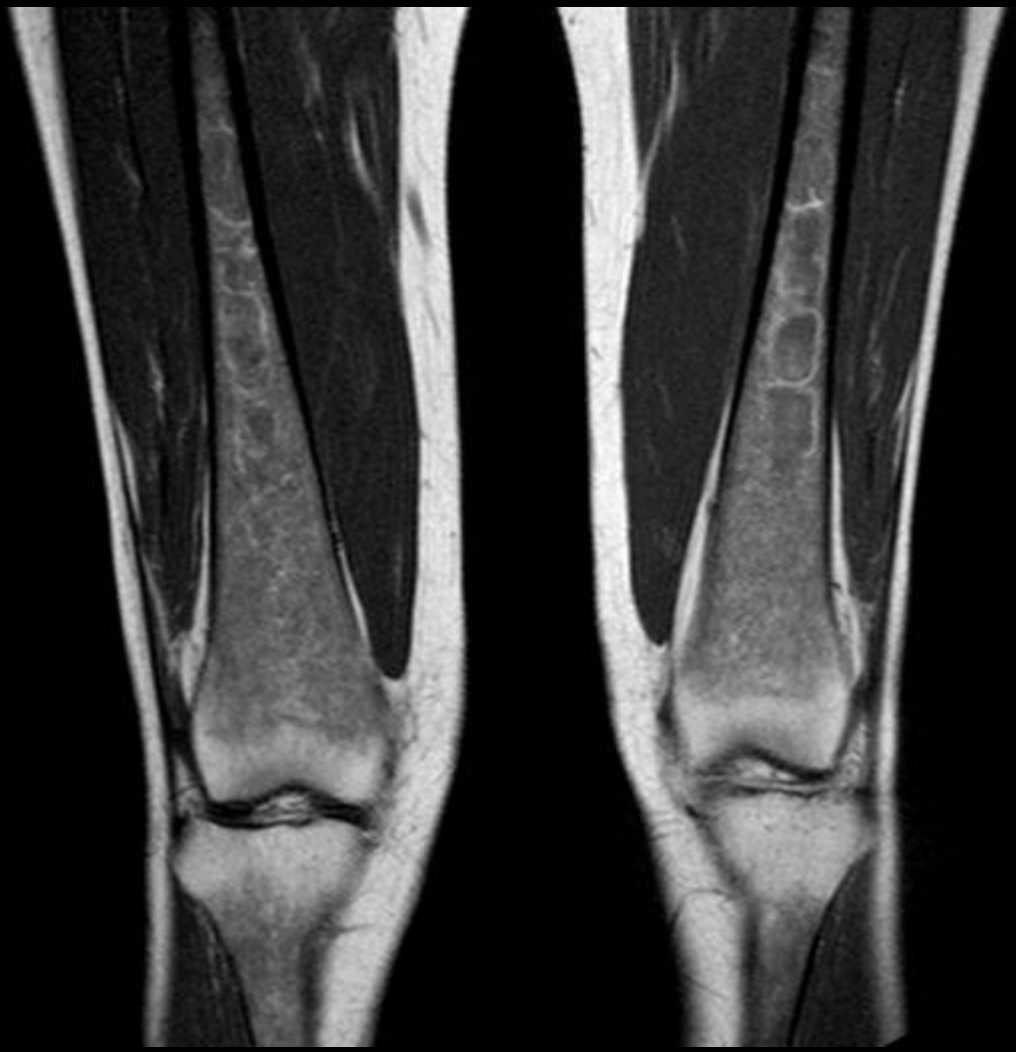
MRI: Femurs



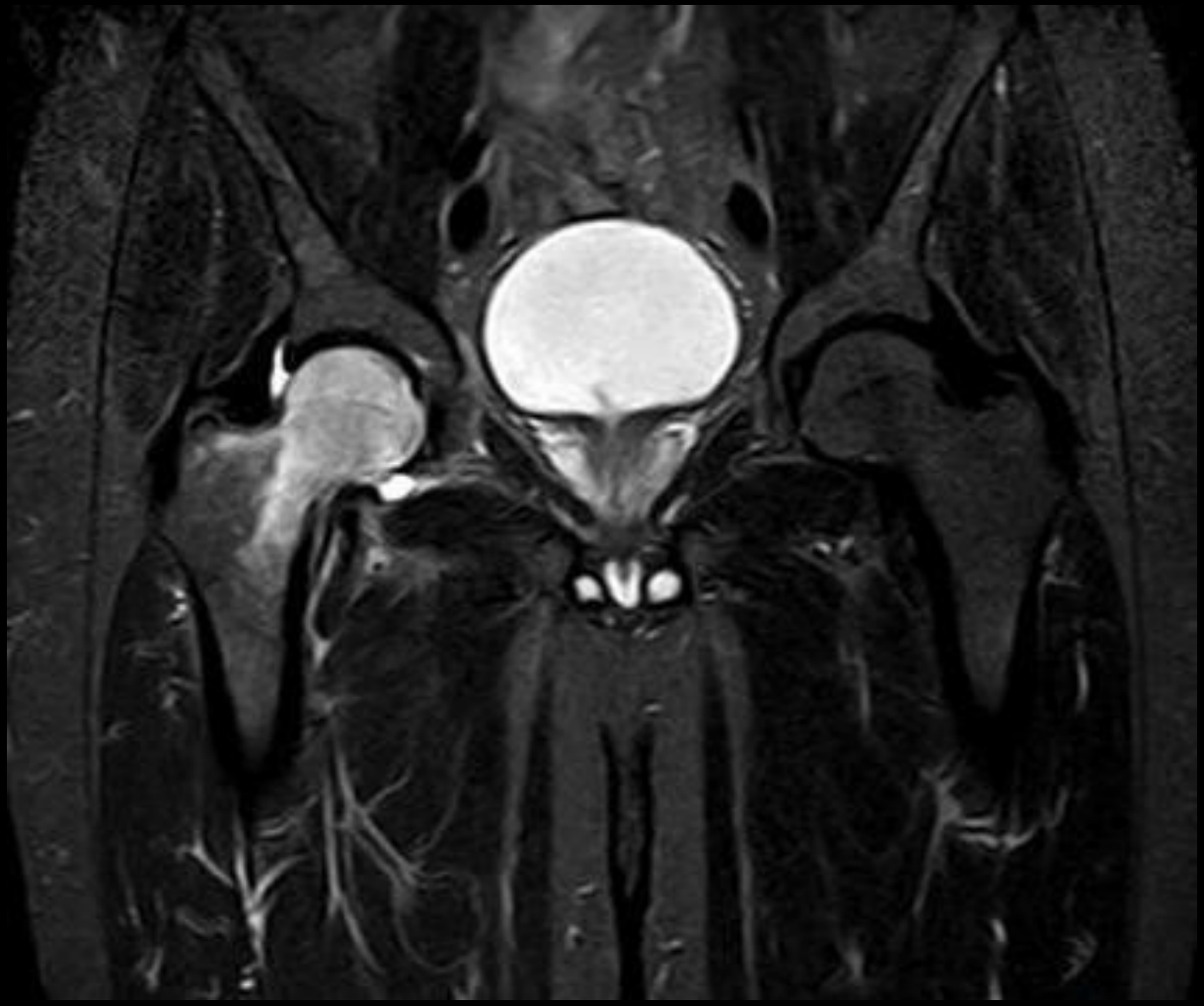
MRI: Lumbar Spine



MRI: Dark Marrow



MRI: Bone Crisis

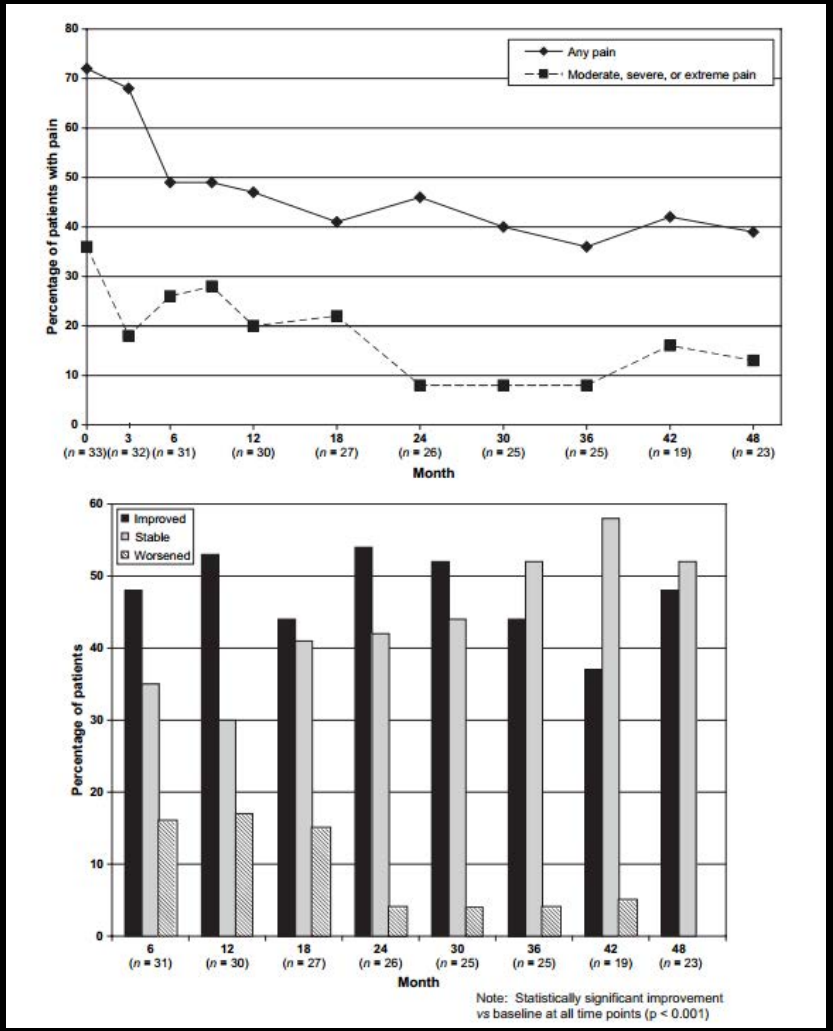


Bone Crisis

- Seen in up to one-third of Gaucher patients
- Acute, severe skeletal pain
- May be accompanied by fever and abnormal lab results
- May show subtle periosteal elevation on radiographs, marrow edema on MRI, or imaging may be normal
- May be difficult to distinguish from subchondral fracture or avascular necrosis in the early phase

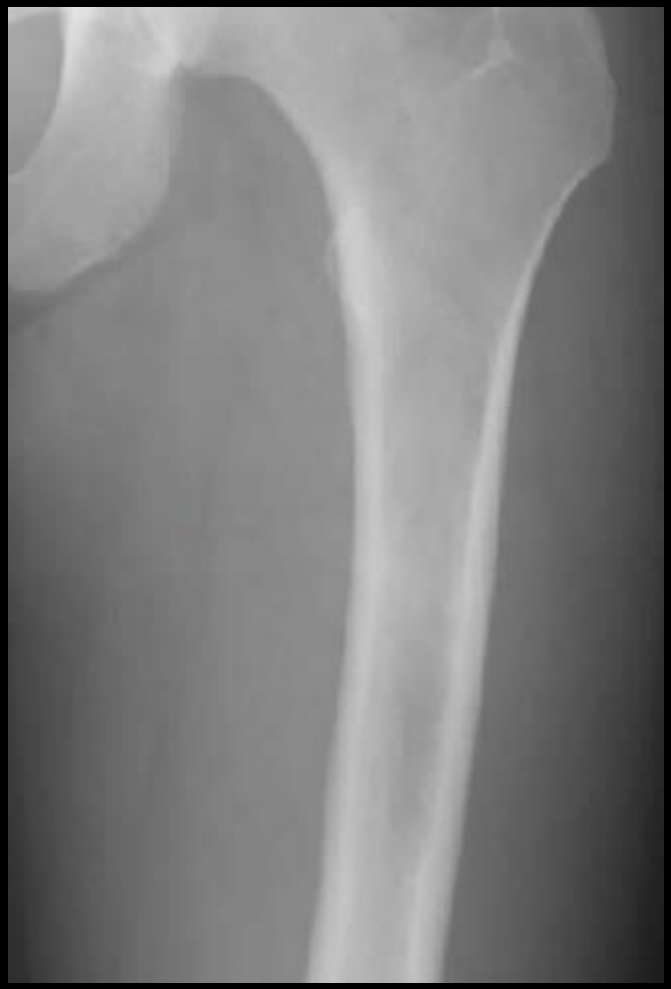
Bone Pain

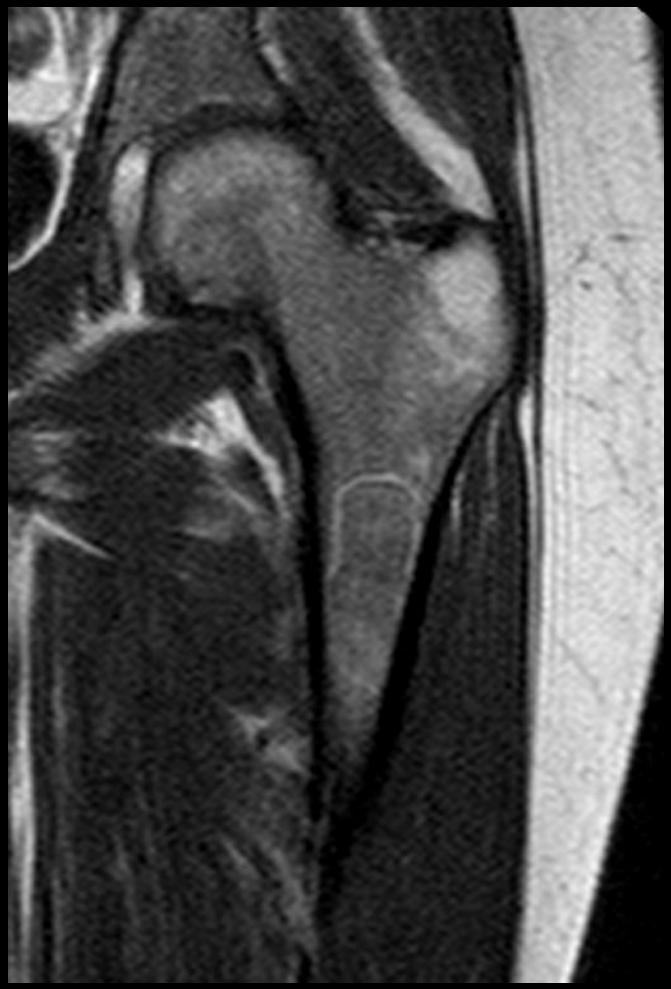
- Bone pain is common in Gaucher disease and does not always have an imaging correlate
- Subjective bone pain does improve with therapy
- Gaucher patients can have bone/joint pain not related to Gaucher



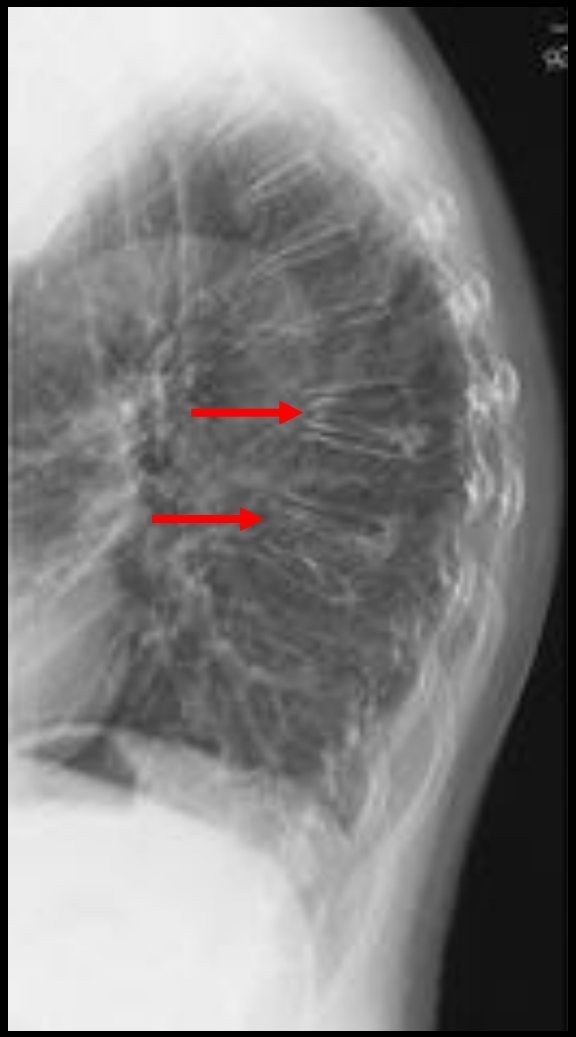
From Sims *et al.*, *Clin Genet.* 2008; 73: 430-440.

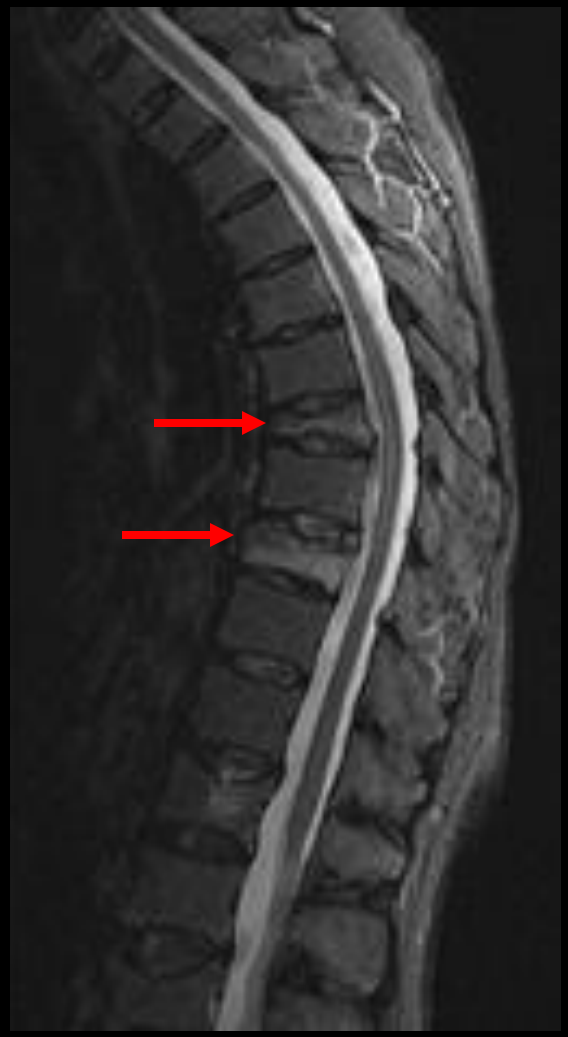
X-Ray vs MRI: Dark Marrow



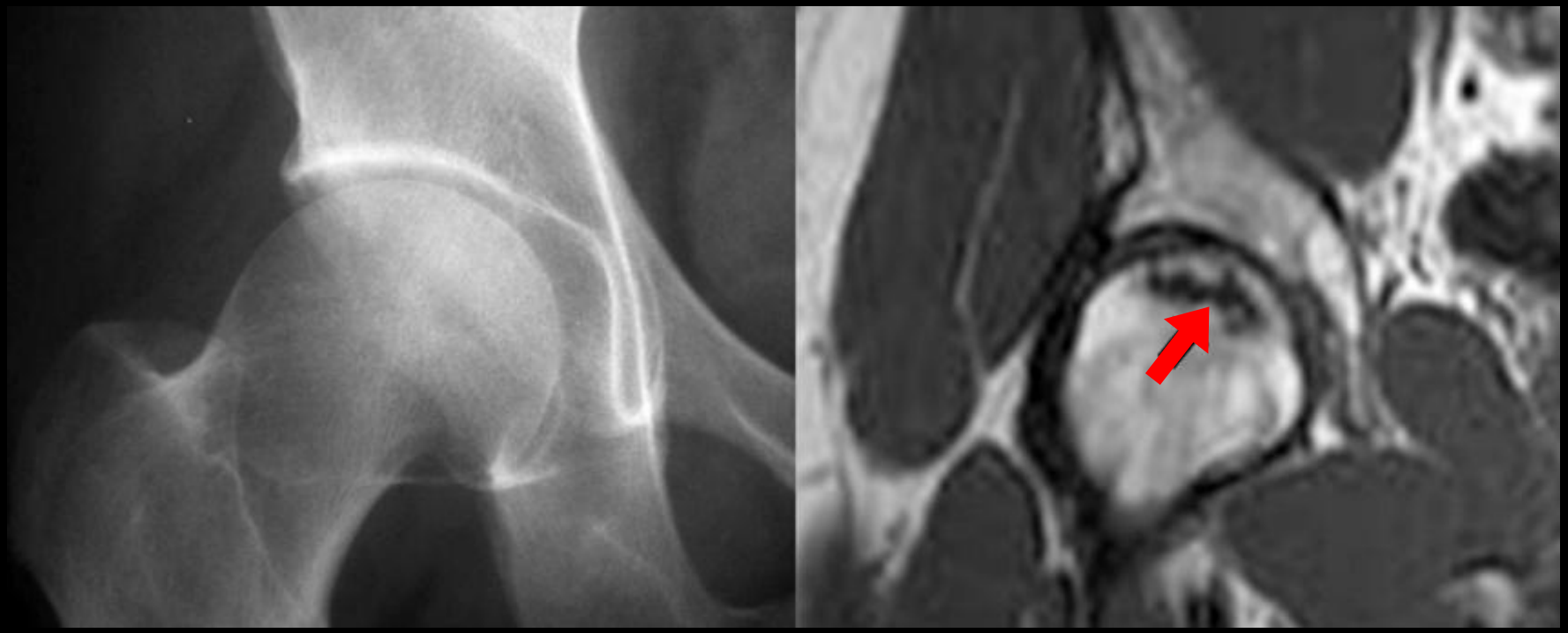


X-Ray vs MRI: Fracture

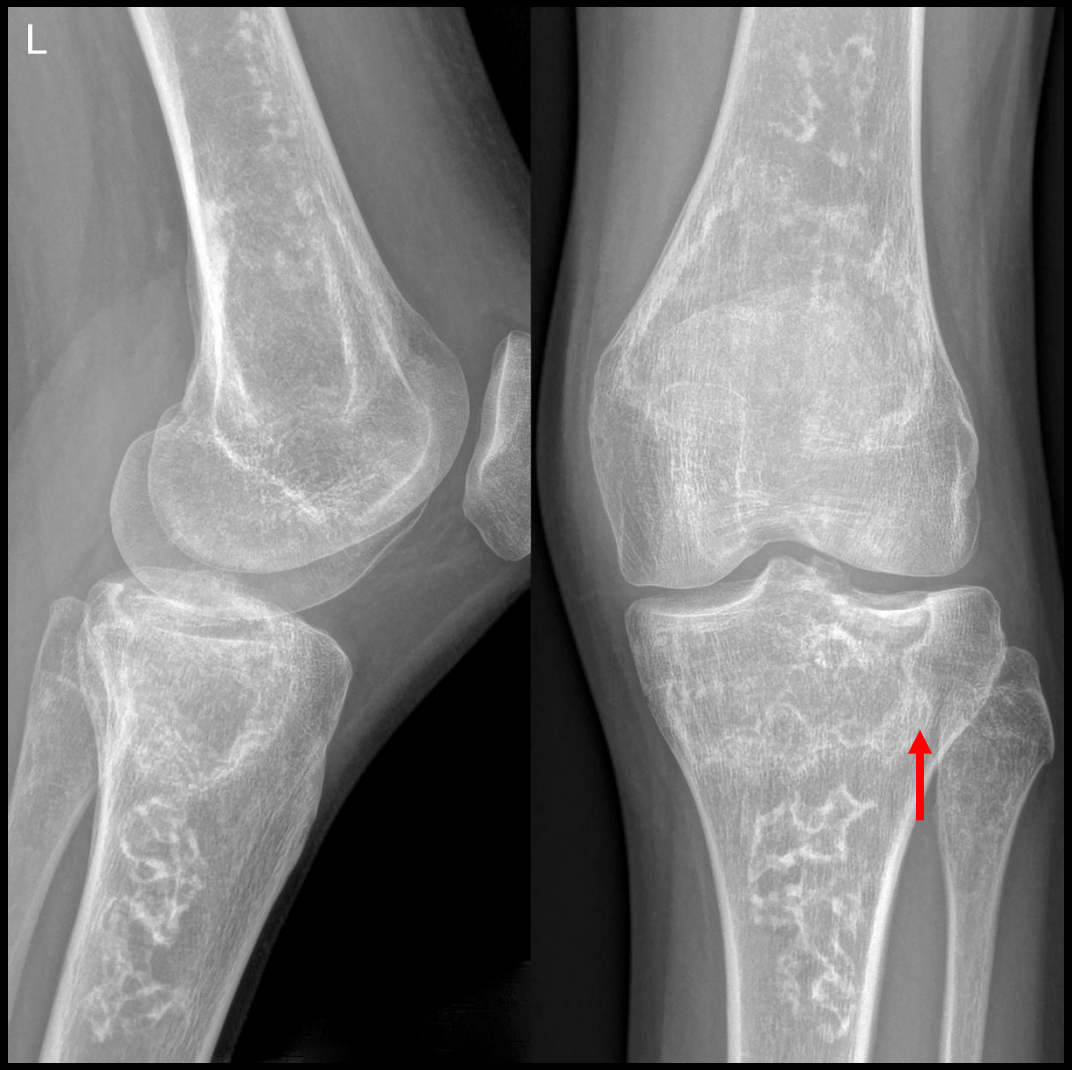




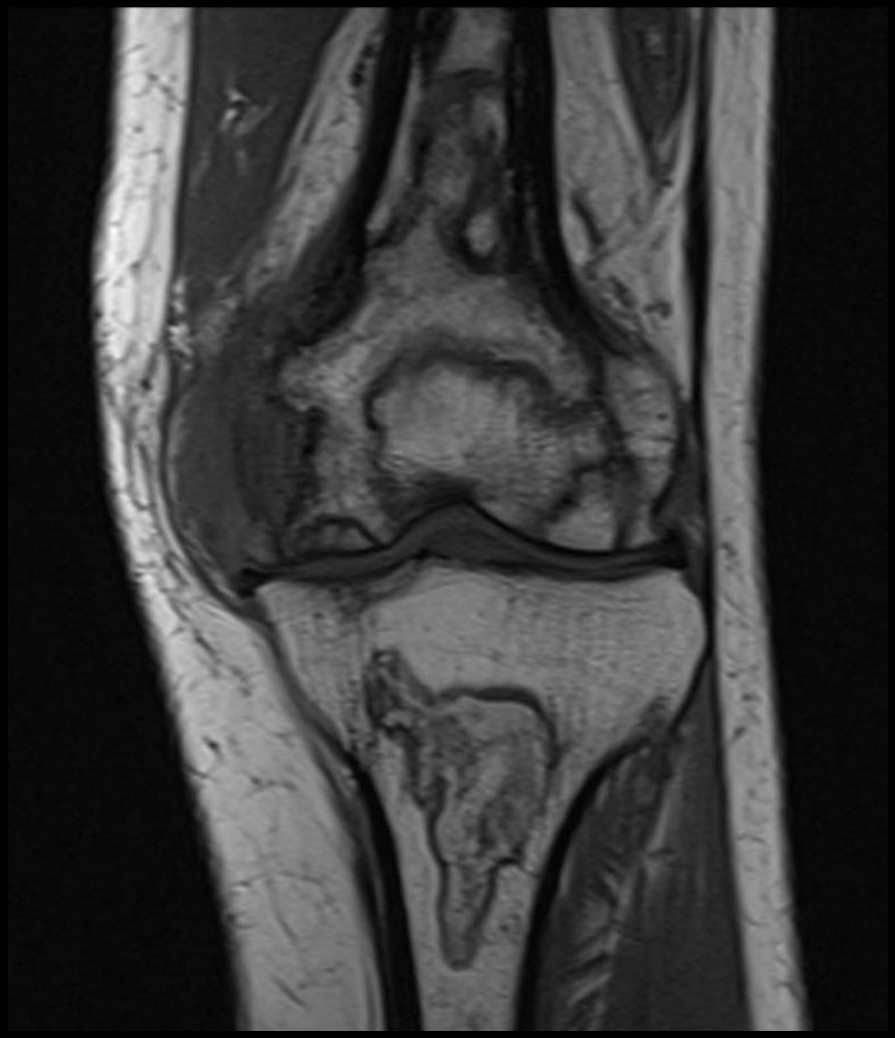
X-Ray vs MRI: Osteonecrosis

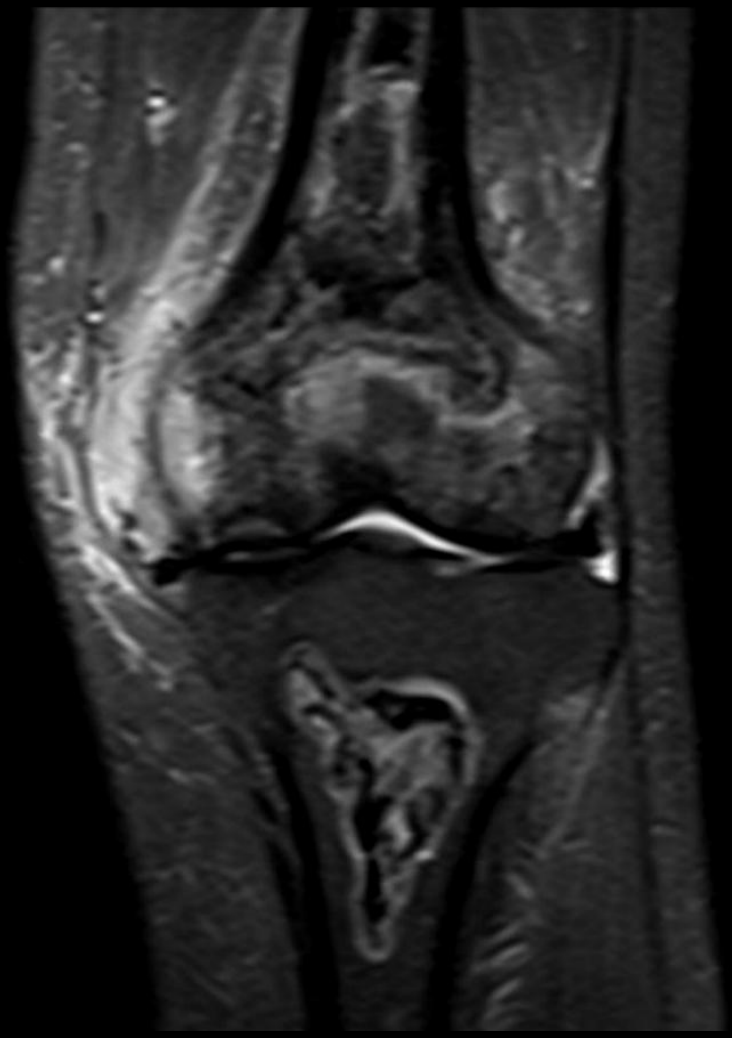


X-Ray vs MRI: Bone Infarct

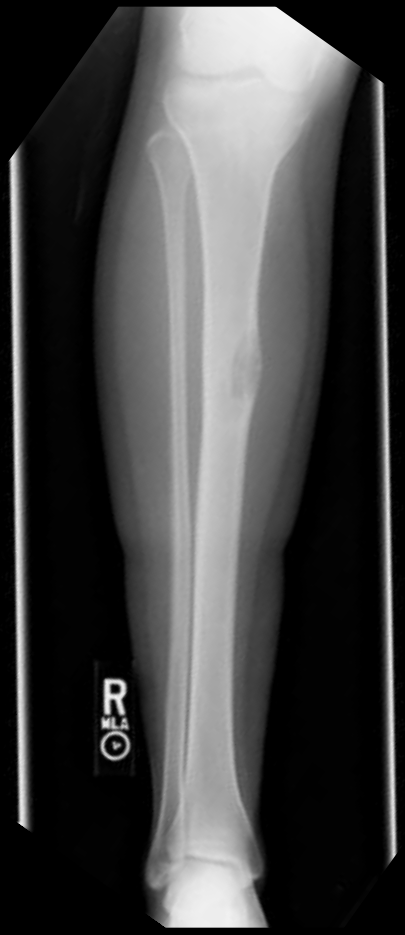


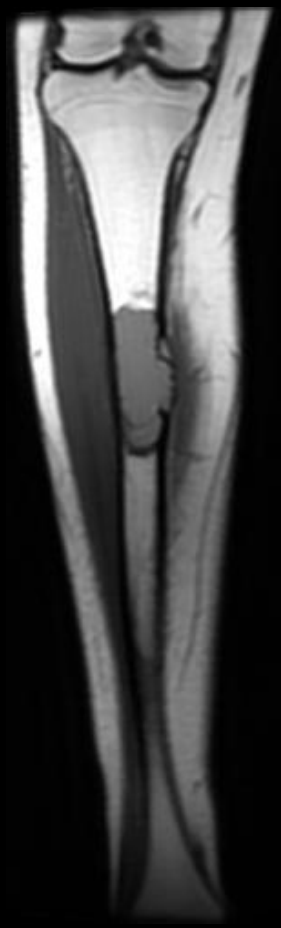
X-Ray vs MRI: Bone Infarct



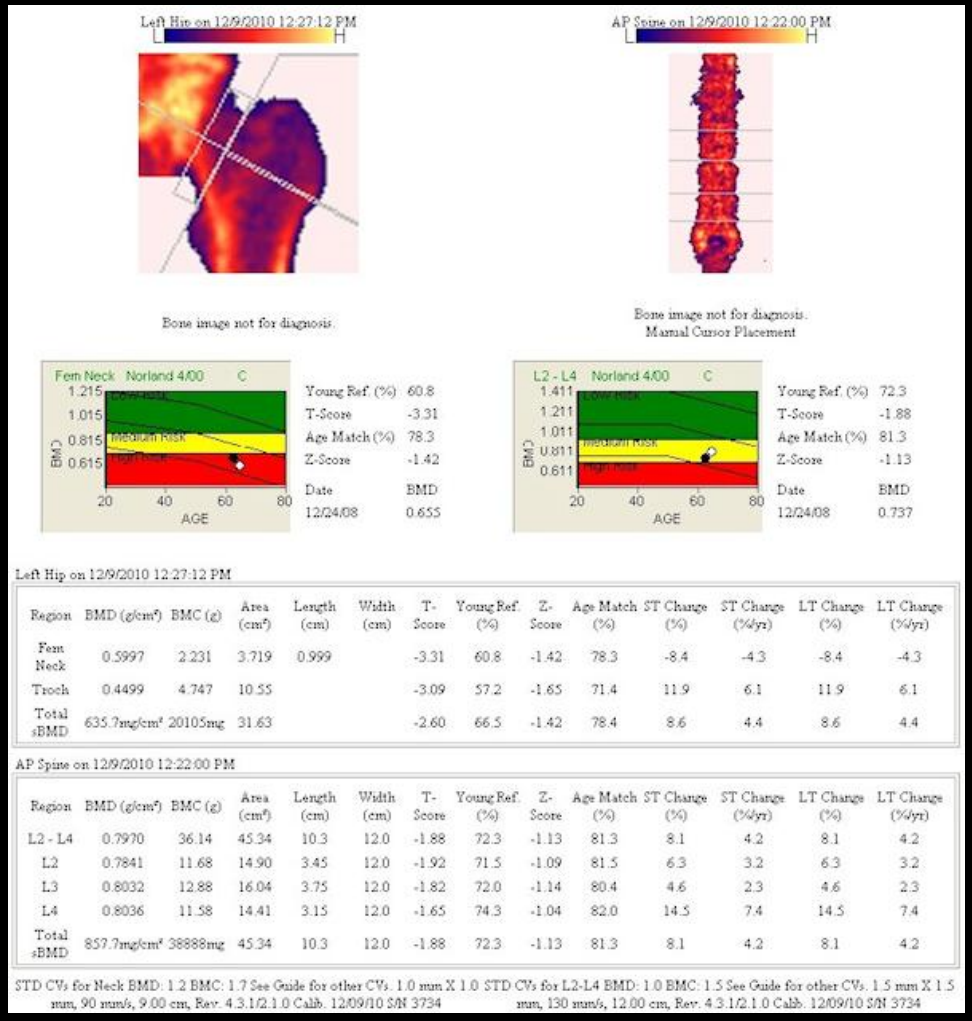


X-Ray vs MRI: Bone Lesion





Dual-Energy X-ray Absorptiometry



Left Hip on 12/9/2010 12:27:12 PM

Region	BMD (g/cm²)	BMC (g)	Area (cm²)	Length (cm)	Width (cm)	T-Score	Young Ref. (%)	Z-Score	Age Match (%)	ST Change (%)	ST Change (%/yr)	LT Change (%)	LT Change (%/yr)
Fem Neck	0.5997	2.231	3.719	0.999		-3.31	60.8	-1.42	78.3	-8.4	-4.3	-8.4	-4.3
Troch	0.4499	4.747	10.55			-3.09	57.2	-1.65	71.4	11.9	6.1	11.9	6.1
Total sBMD	635.7mg/cm²	20105mg	31.63			-2.60	66.5	-1.42	78.4	8.6	4.4	8.6	4.4

AP Spine on 12/9/2010 12:22:00 PM

Region	BMD (g/cm²)	BMC (g)	Area (cm²)	Length (cm)	Width (cm)	T-Score	Young Ref. (%)	Z-Score	Age Match (%)	ST Change (%)	ST Change (%/yr)	LT Change (%)	LT Change (%/yr)
L2 - L4	0.7970	36.14	45.34	10.3	12.0	-1.88	72.3	-1.13	81.3	8.1	4.2	8.1	4.2
L2	0.7841	11.68	14.90	3.45	12.0	-1.92	71.5	-1.09	81.5	6.3	3.2	6.3	3.2
L3	0.8032	12.88	16.04	3.75	12.0	-1.82	72.0	-1.14	80.4	4.6	2.3	4.6	2.3
L4	0.8036	11.58	14.41	3.15	12.0	-1.65	74.3	-1.04	82.0	14.5	7.4	14.5	7.4
Total sBMD	857.7mg/cm²	38888mg	45.34	10.3	12.0	-1.88	72.3	-1.13	81.3	8.1	4.2	8.1	4.2

STD CVs for Neck BMD: 1.2 BMC: 1.7 See Guide for other CVs. 1.0 mm X 1.0 mm, 90 mm/s, 9.00 cm, Rev. 4 3.1/2.1.0 Calib. 12/09/10 S/N 3734

STD CVs for L2-L4 BMD: 1.0 BMC: 1.5 See Guide for other CVs. 1.5 mm X 1.5 mm, 130 mm/s, 12.00 cm, Rev. 4 3.1/2.1.0 Calib. 12/09/10 S/N 3734

Dual-Energy X-ray Absorptiometry

Classification	T-Score Value
Normal bone mass	≥-1.0
Low bone mass (osteopenia)	-1.0 to -2.5
Osteoporosis	≤-2.5

T-score compares bone density with the average bone density of **young, healthy adults** of the same sex

Z-Score	Classification
More than -2	**Normal**
-2 or less	**Below Normal**

Z-score compares a person's bone density with the average bone density of other people of **the same age, sex, and body size**

Gaucher Bone Imaging Summary

Radiographs (X-rays)	MRI	DEXA
Bone crisis	Bone crisis	
Pathologic fracture	Pathologic fracture	
Osteonecrosis	Osteonecrosis	
Lytic lesions	Lytic lesions	
Bone remodeling (e.g. Erlenmeyer flask deformity)	Bone remodeling (e.g. Erlenmeyer flask deformity)	
Hardware/prosthesis imaging	Hardware/prosthesis imaging	
Cortical thinning/tunneling (osteopenia)	**Dark marrow** (and quantitative imaging)	**Bone mineral density** (osteopenia/osteoporosis)

Outline

- Introduction to lysosomal storage disorders (LSDs)
- Imaging of skeletal abnormalities in LSDs
  - MPS (dysostosis multiplex)
  - Pyknodysostosis
  - Gaucher disease
- **Management of bone abnormalities in LSDs**
  - Role of the orthopedic surgeon
- Recent developments
- Q&A

Management of LSD Bone Disease

- Treatment is focused on the underlying cause of the disease, replacing or enhancing the missing or deficient enzyme or shifting the balance between substrate and product
  - Enzyme replacement therapy (ERT)
  - Substrate reduction therapy (SRT)
  - Pharmacologic chaperone therapy (PCT)
  - Hematopoietic stem cell transplantation (HSCT)
  - New/emerging therapies, including gene therapy and genome editing

Management of LSD Bone Disease

- Current treatments available for MPS:

MPS type	Common name	Gene	GAG	ERT/HSCT
MPS I	Hurler, H–S, Sheie	*IDUA*	DS, HS	+/+
MPS II	Hunter	*IDS*	DS, HS	+/−
MPS III	Sanfilippo A,B,C,D	*GNS, HGSNAT, NAGLU, SGSH*	HS	−/−
MPS IV	Morquio A,B	*GALNS* *GLB1*	KS, CS KS	+/−
MPS VI	Marateaux-Lamy	*ARSB*	DS	+/−
MPS VII	Sly	*GUSB*	DS, HS, CS	+/−
MPS IX	Hyaluronidase deficiency	*HYAL1*	HA	−/−

MPS mucopolysaccharidoses, HS Heparan sulfate, DS dermatan sulfate, KS keratan sulfate, CS chondroitin sulfate, HA hyaluronic acid, H–S Hurler–Sheie, ERT enzyme replacement therapy, HSCT hematopoietic stem cell transplantion.

From Penon-Portmann *et al.*, *Pediatr Neonat.* 2025; S1: S10-17.

Management of LSD Bone Disease

- Current treatments available for Gaucher disease:
  - Enzyme replacement therapy (ERT)
  - Substrate reduction therapy (SRT)
  - Gene therapy (clinical trials)

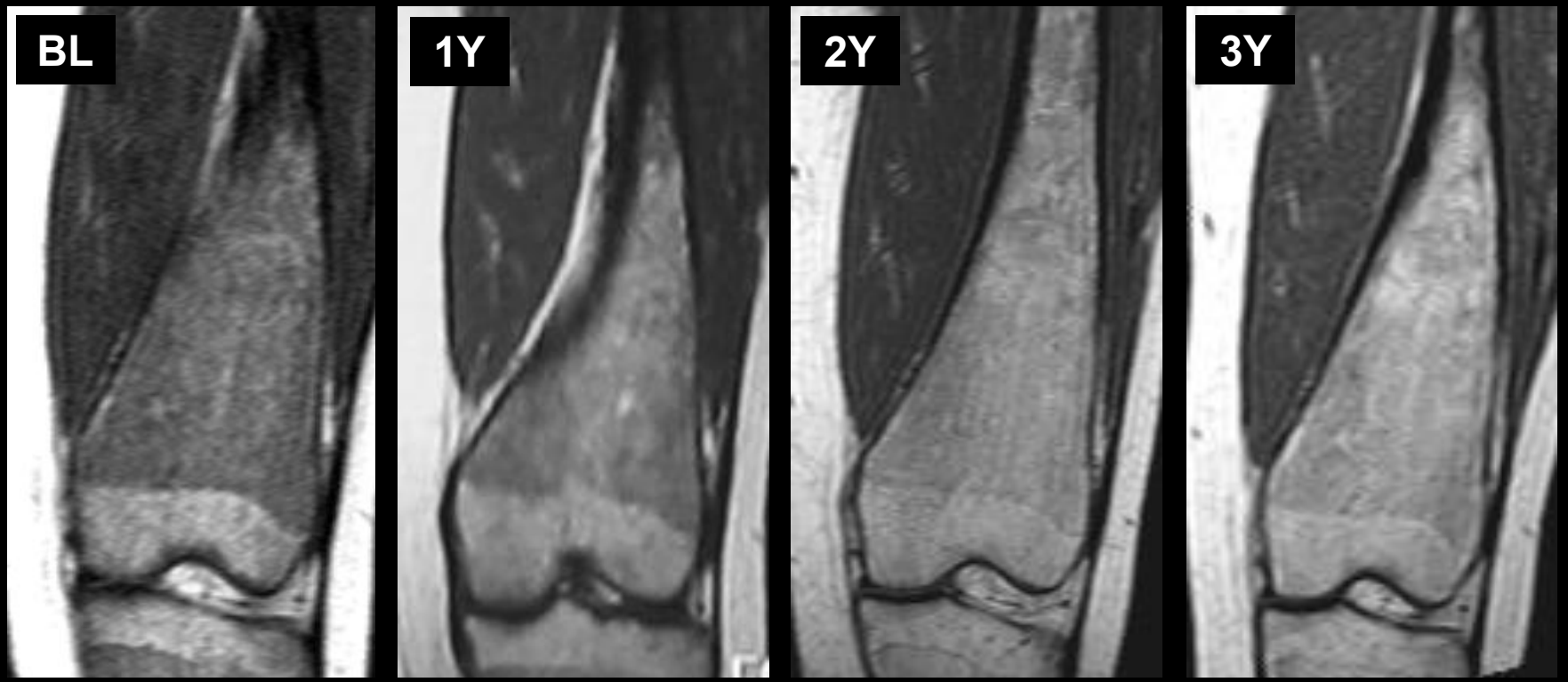
Management of LSD Bone Disease

- This is supplemented by supportive care targeting specific aspects of disease presentation
  - Anti-inflammatory agents
  - Medications to increase/inhibit bone formation
  - Orthopedic procedures to deal with severe/irreversible skeletal complications
  - Other medications and treatments for non-skeletal disease manifestations

Management of LSD Bone Disease

- Studies show improvement in symptoms and quality of life with treatment for patients with LSDs
- However, skeletal problems are notably refractory to therapy, and some skeletal complications are irreversible
- Bone changes in response to therapy have been most thoroughly studied for Gaucher disease

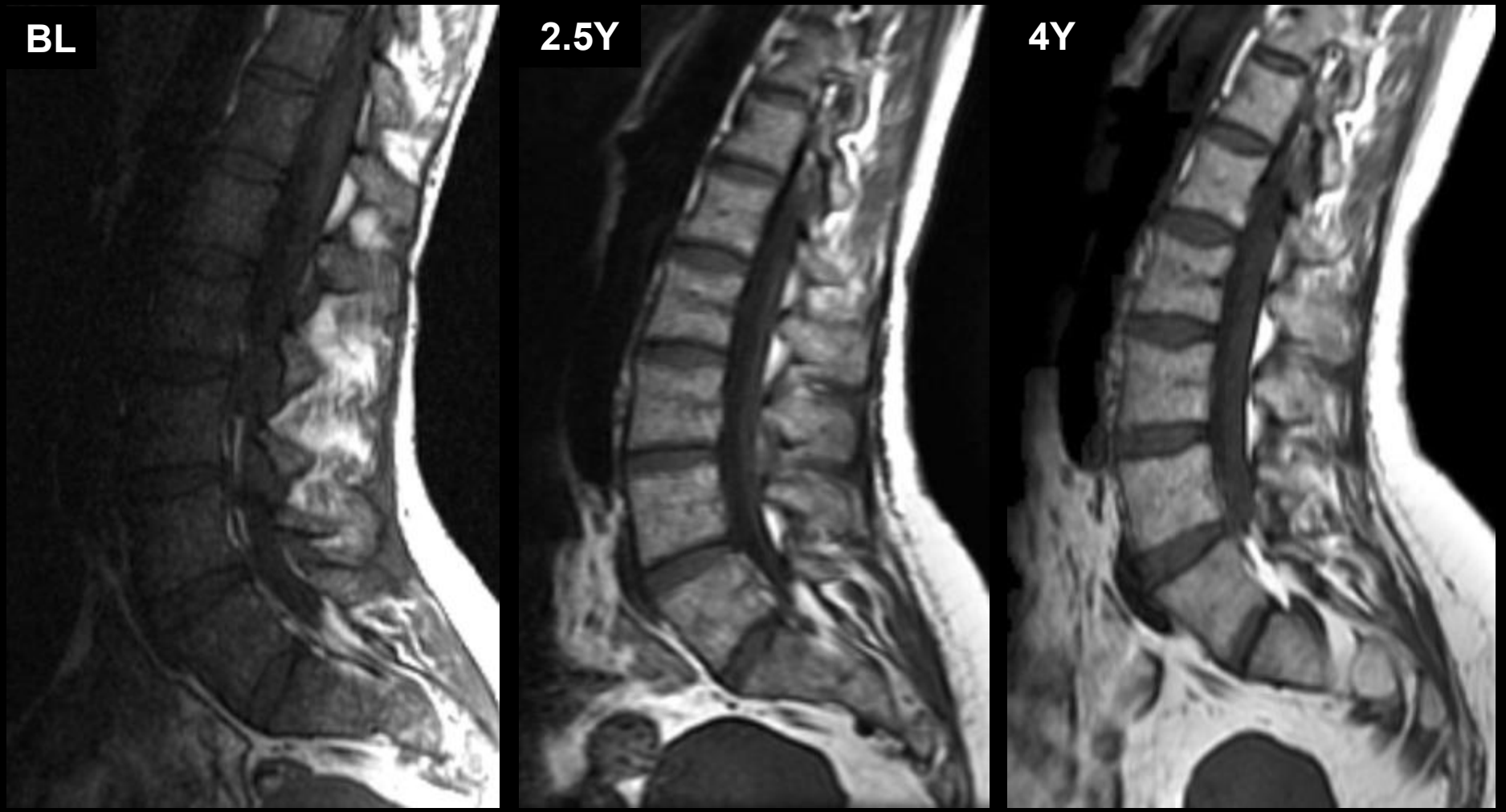
Gaucher Marrow with Therapy



Roughly 60-70% of patients demonstrate bone marrow improvement with medical treatment

From Kamath *et al.*, *Skel Radiol* 2014; 43: 1353-1360.

Gaucher Marrow with Therapy



From Robertson *et al.*, *AJR* 2007; 188: 1521-1528.

Gaucher BMD with Therapy

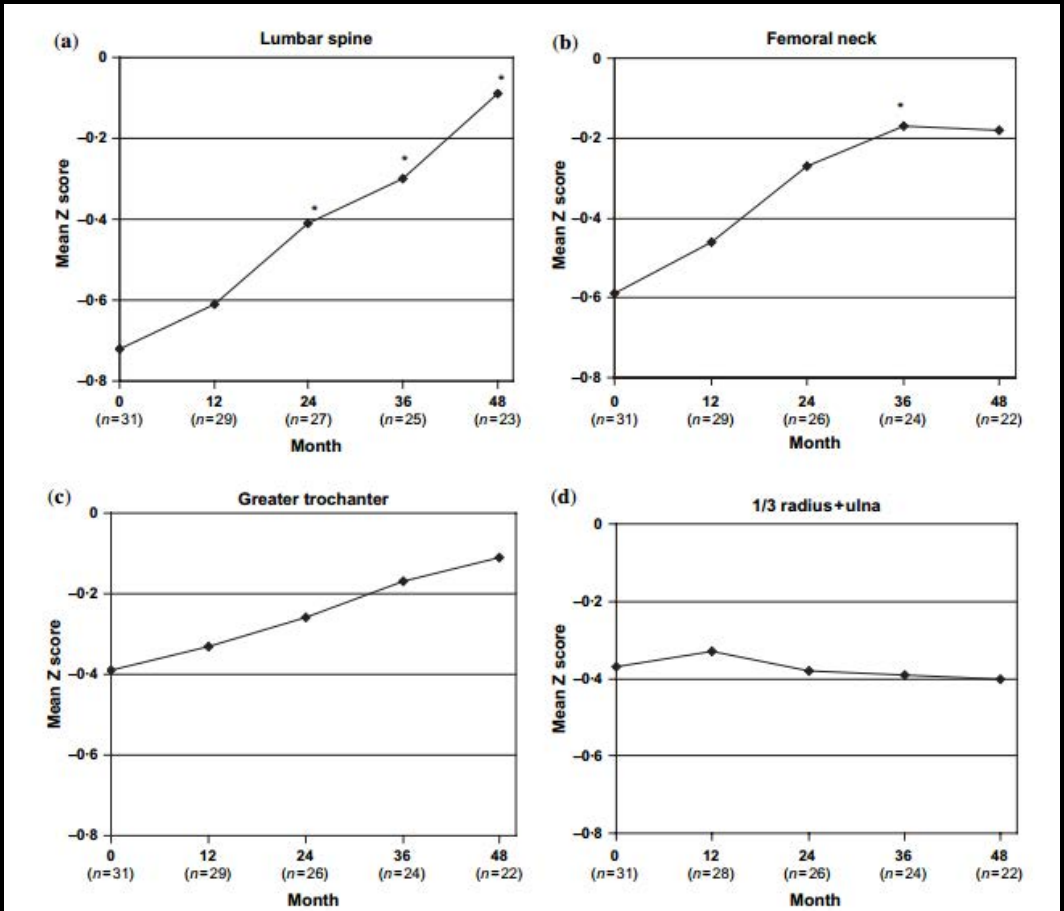
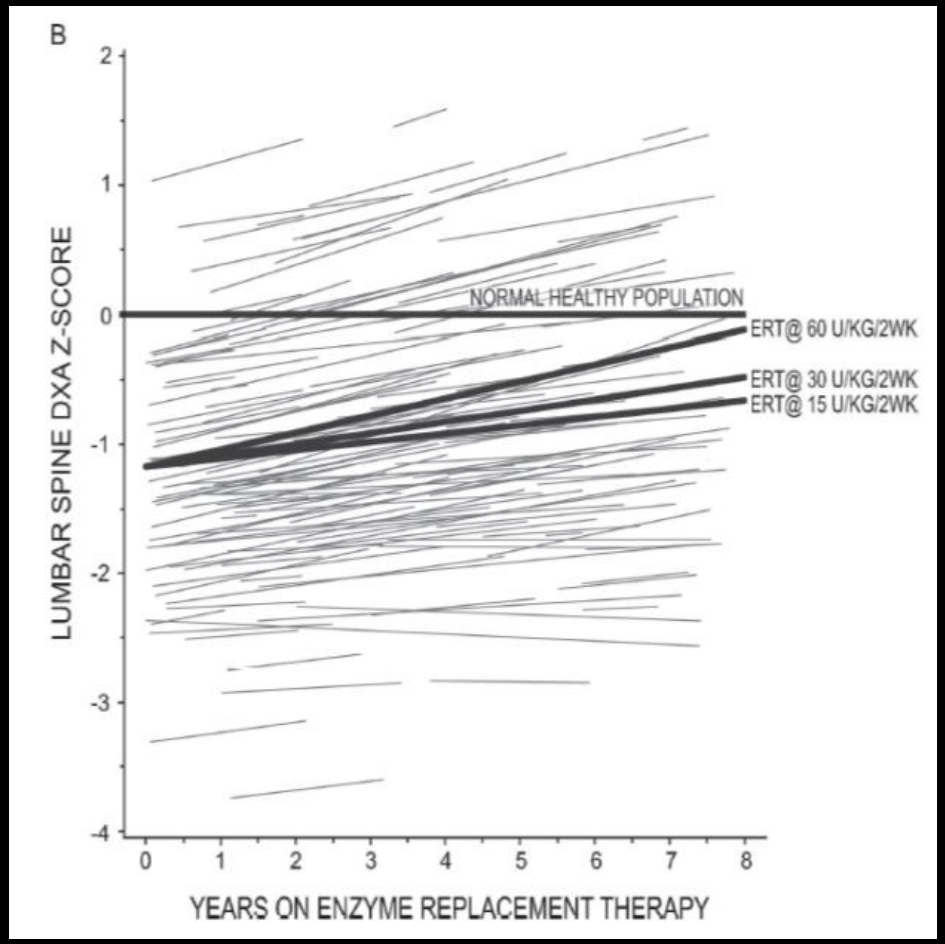


Fig. 2. Bone density (mean dual-energy X-ray absorptiometry Z scores, reflective of age-adjusted normal) as measured in the spine (**a**), femoral neck (**b**), greater trochanter (**c**), and 1/3 radius + ulna (**d**). P values test the hypothesis that the mean change is equal to zero (*t*-test). *$p < 0.05$.

From Sims *et al.*, *Clin Genet.* 2008; 73: 430-440.

Gaucher BMD with Therapy



From Wenstrup *et al.*, *JBMR* 2008; 22: 119-126.

Imaging Surveillance for Gaucher

Image test	Patients not on therapy	Patients on therapy		
		Not achieved therapeutic goals	Achieved therapeutic goals	At time of dose change or significant clinical complication
	Every 12-24 months	**Every 12 months**	**Every 12-24 months**	
MRI (coronal; T1- and T2-weighted) of entire femora[a]	✕	✕	✕	✕
X-ray[b]	✕	✕	✕	✕
DEXA[c]	✕	✕	✕	✕

From the International Collaborative Gaucher Group (ICGC) Gaucher Registry.

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- Recent developments
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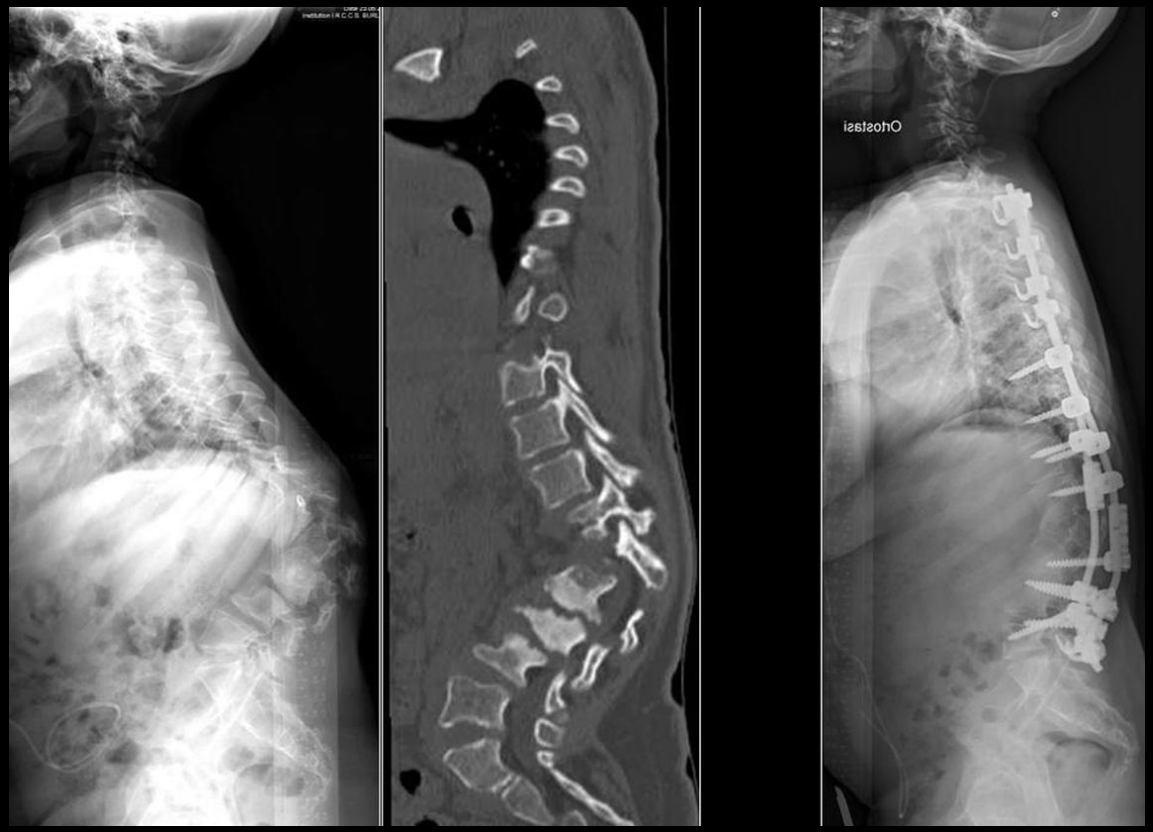
Orthopedic Care in MPS

- Procedures focus on severe/irreversible skeletal complications to improve quality of life
- Most common surgical procedure is carpal tunnel and trigger finger release (sometimes in children)
- Soft tissue surgery for release of joint contractures is sometimes performed, but outcomes have been poor
- Spinal fusion may be needed to treat thoracic kyphoscoliosis and atlantoaxial instability
- Corrective surgery for hip subluxation, genu valgum, and ankle valgus (e.g. pelvic, femoral, or tibial osteotomy)
- Hip or knee arthroplasty may eventually be needed

Orthopedic Care in MPS

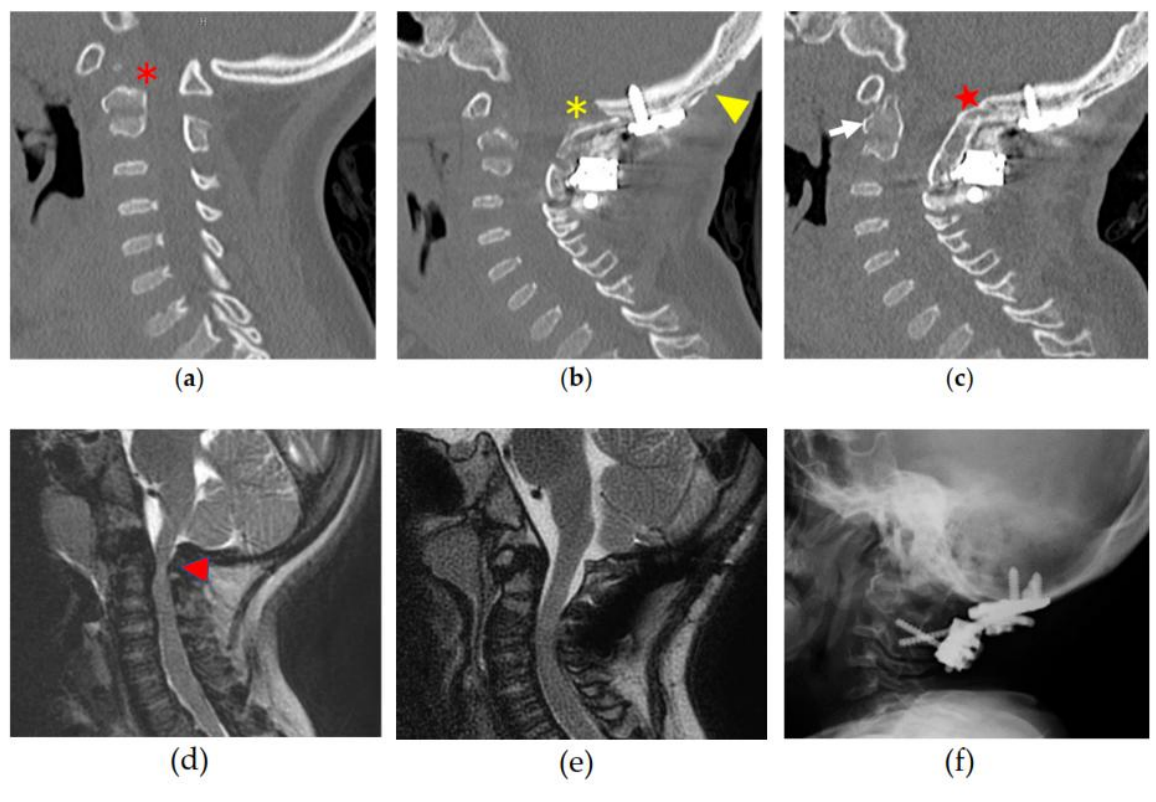
- Spinal fusion to treat kyphoscoliosis in MPS I



From Borgo *et al*. *Ital J Pediatr* 2018; 44: Suppl 2, 123.

Orthopedic Care in MPS

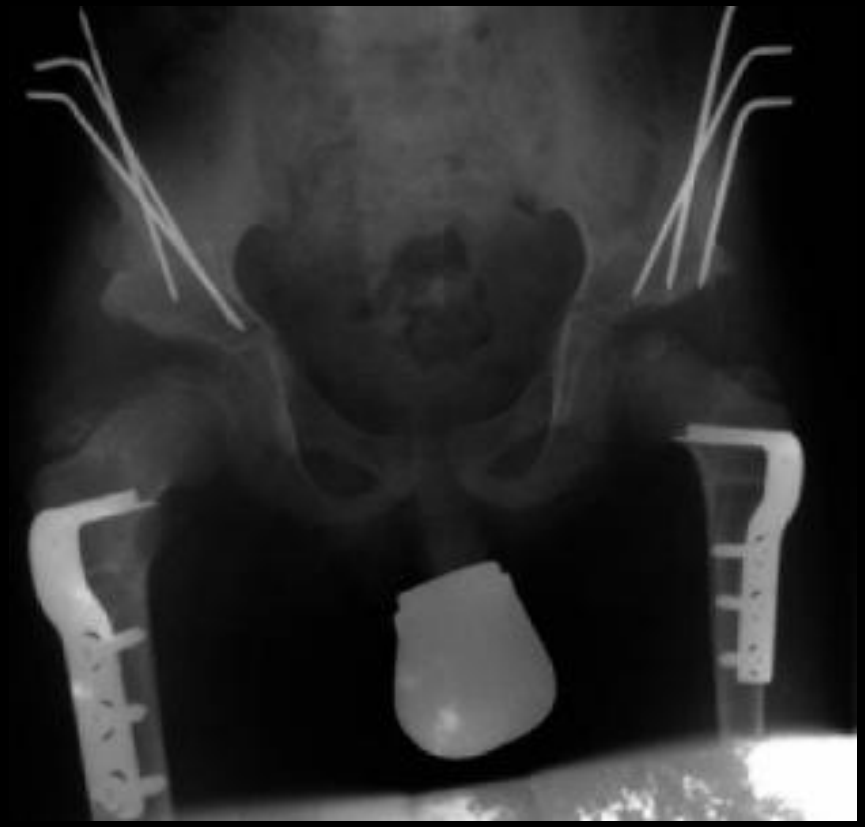
- Occipitocervical fusion for atlantoaxial instability in MPS IVa



From Terai and Nakamura. *Int J Mol Sci 2020*; 21: 1171.

Orthopedic Care in MPS

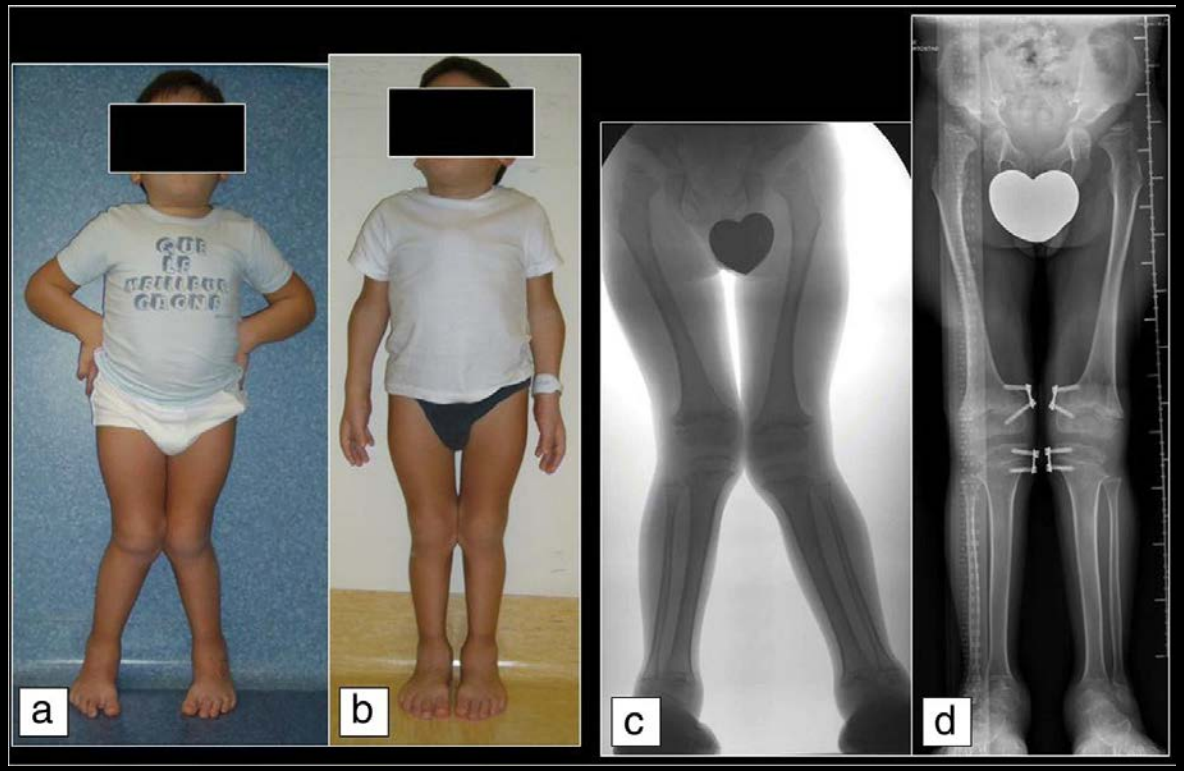
- Hip osteotomies for patient with MPS IVb



From van den Eeden *et al*. *Case Rep Orthop* 2021; 2021: 5584408.

Orthopedic Care in MPS

- Bilateral temporary hemiepiphysiodesis of femur and tibia to correct genu valgum in a child with MPS IVa

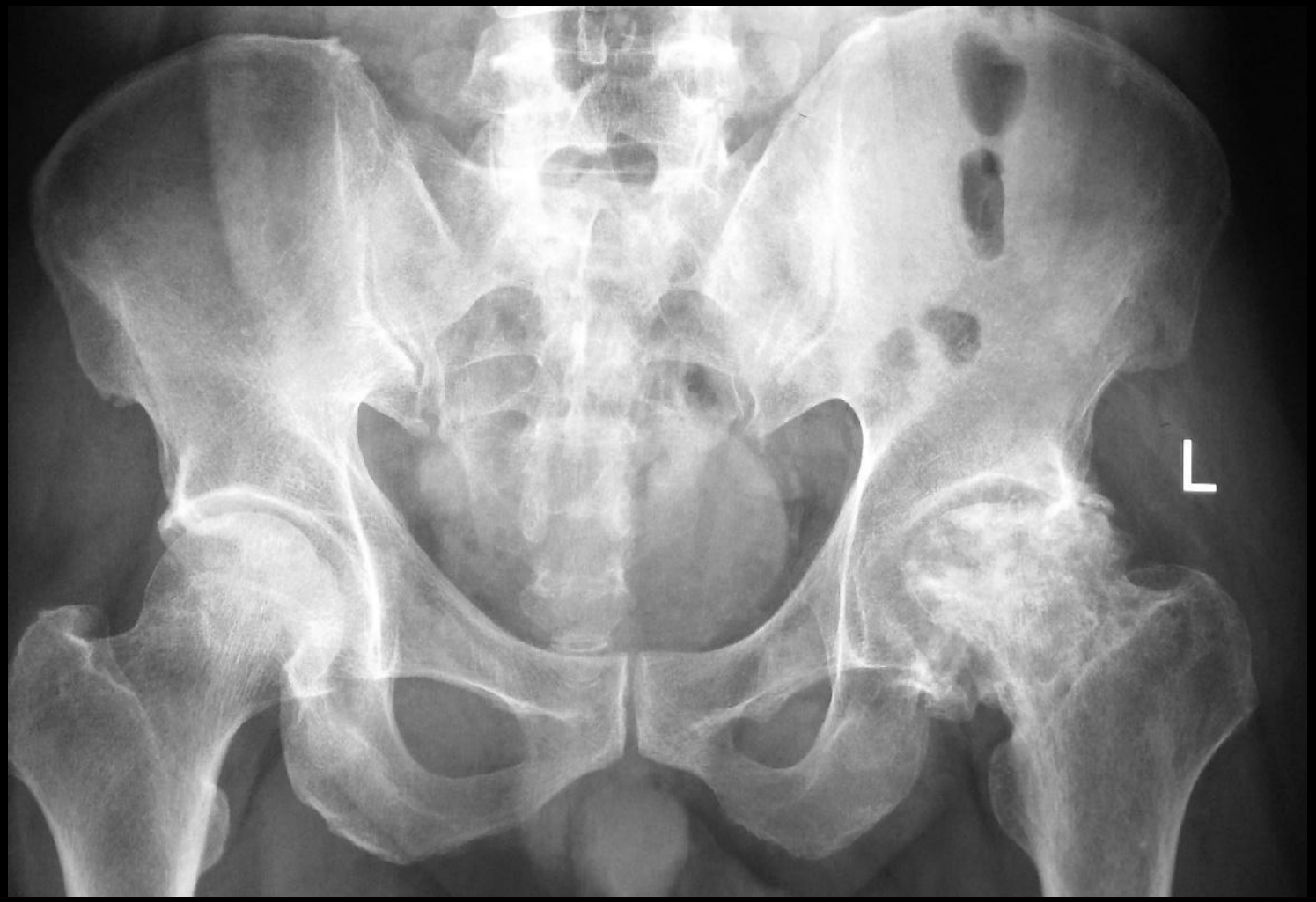


From Borgo *et al*. *Ital J Pediatr* 2018; 44: Suppl 2, 123.

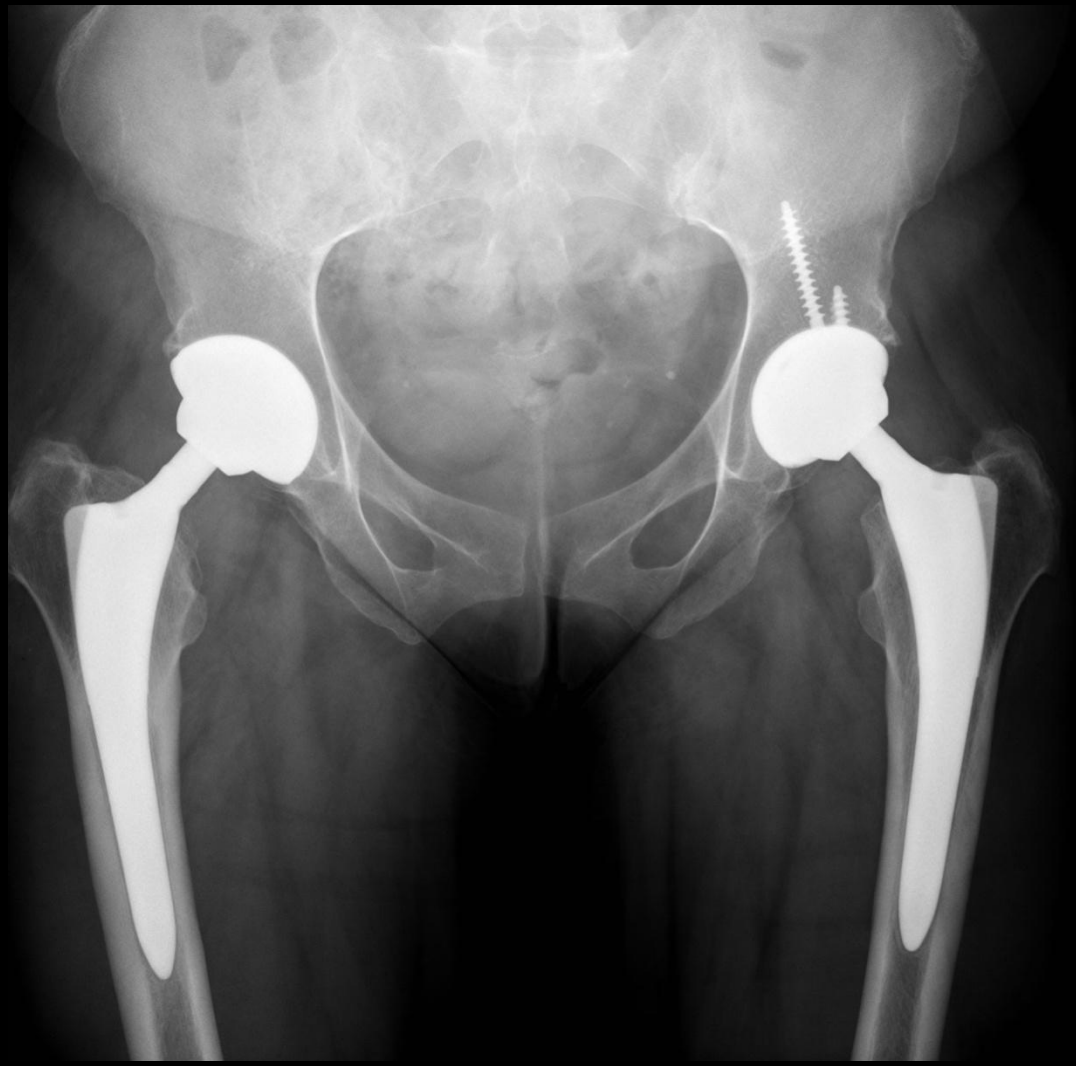
Orthopedic Care in Gaucher

- As for MPS, procedures focus on severe/irreversible skeletal complications to improve quality of life
- Hip arthroplasty for femoral head osteonecrosis
- Surgery to address structural abnormalities of the spine
- Fixation of fractures
- Prophylactic fixation of bone lesions at risk for pathologic fracture
- Important to remember that Gaucher patients have additional risks due to bone weakness, delayed healing, and bleeding problems

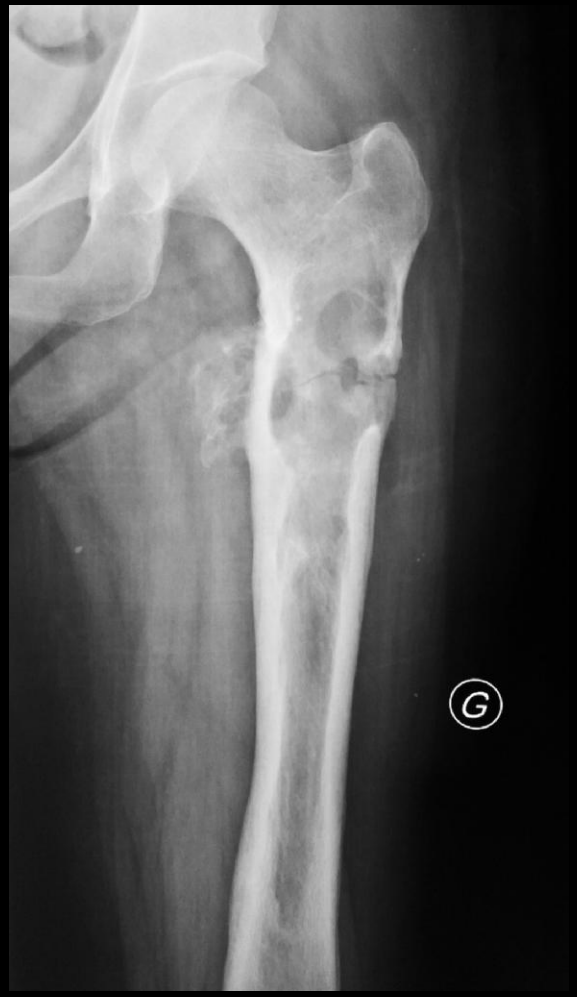
Prostheses for Osteonecrosis



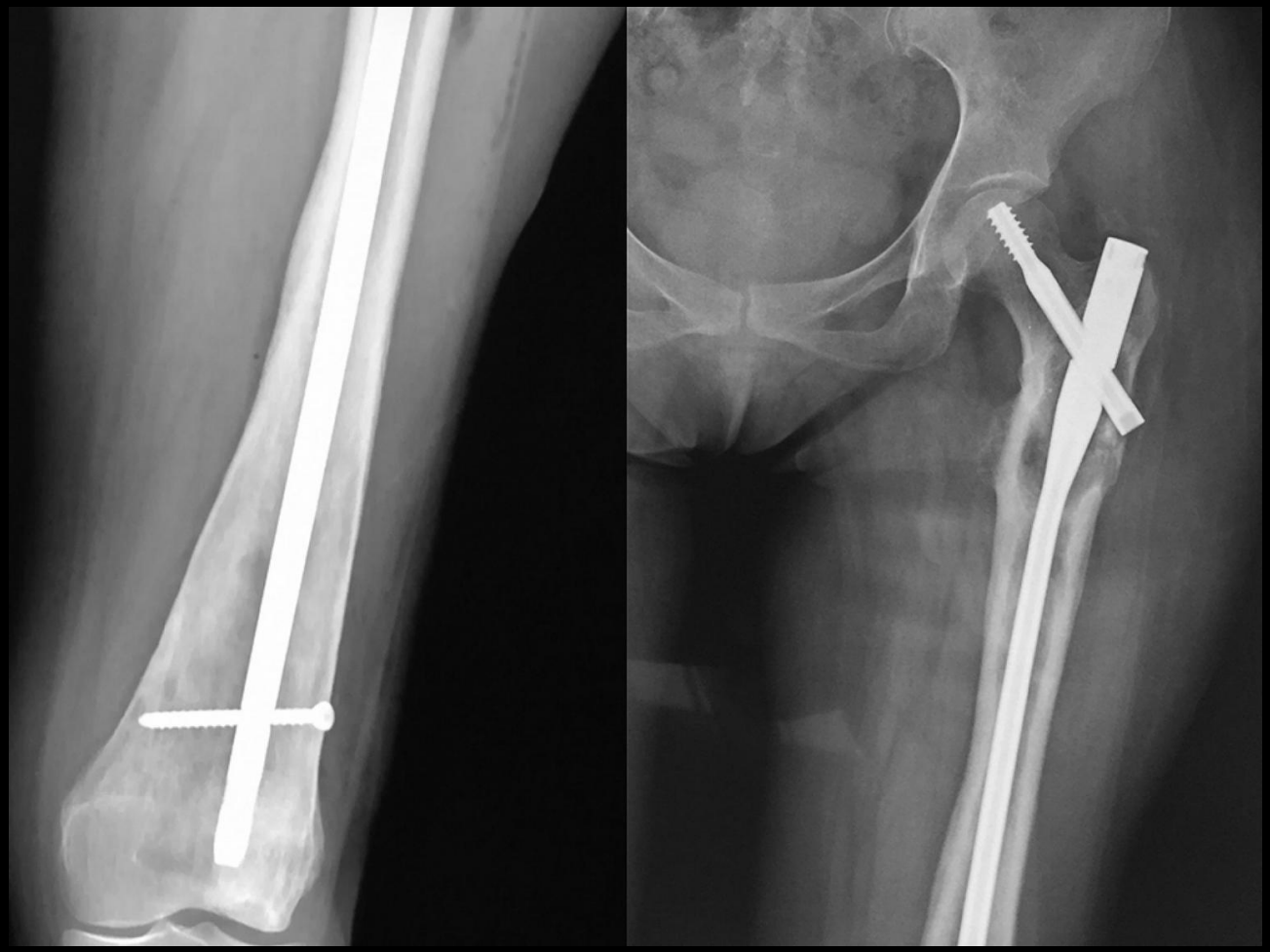
Prostheses for Osteonecrosis



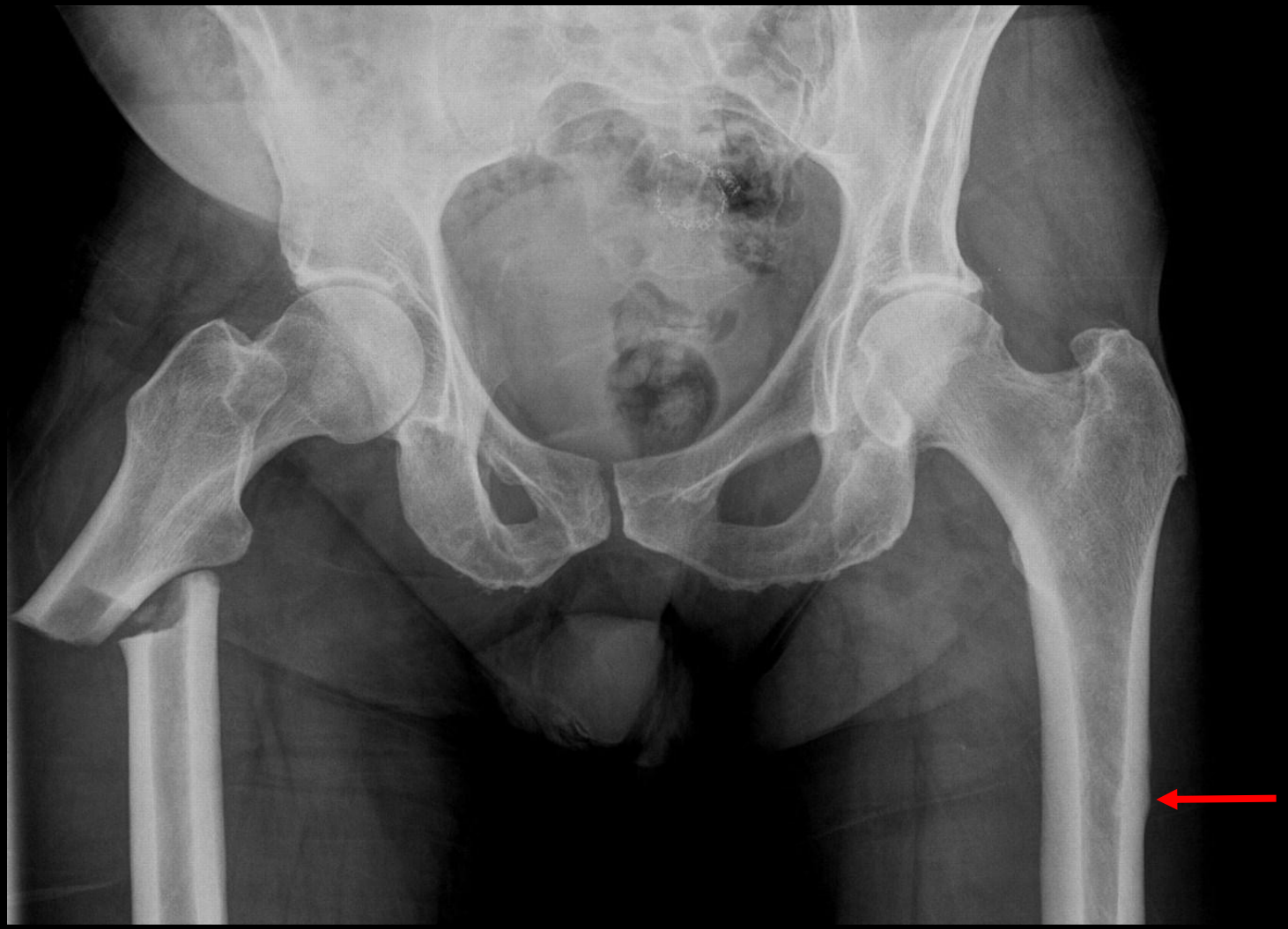
Pathologic Fracture Fixation



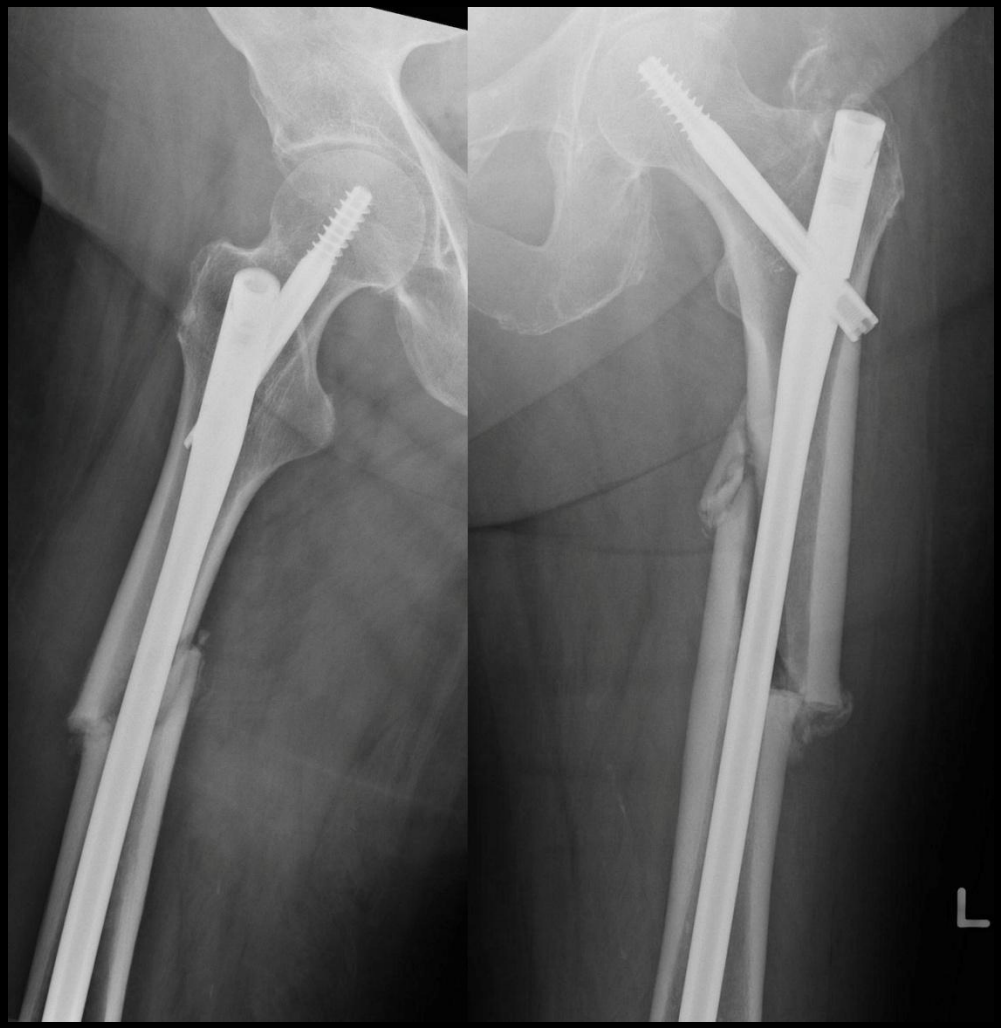
Pathologic Fracture Fixation



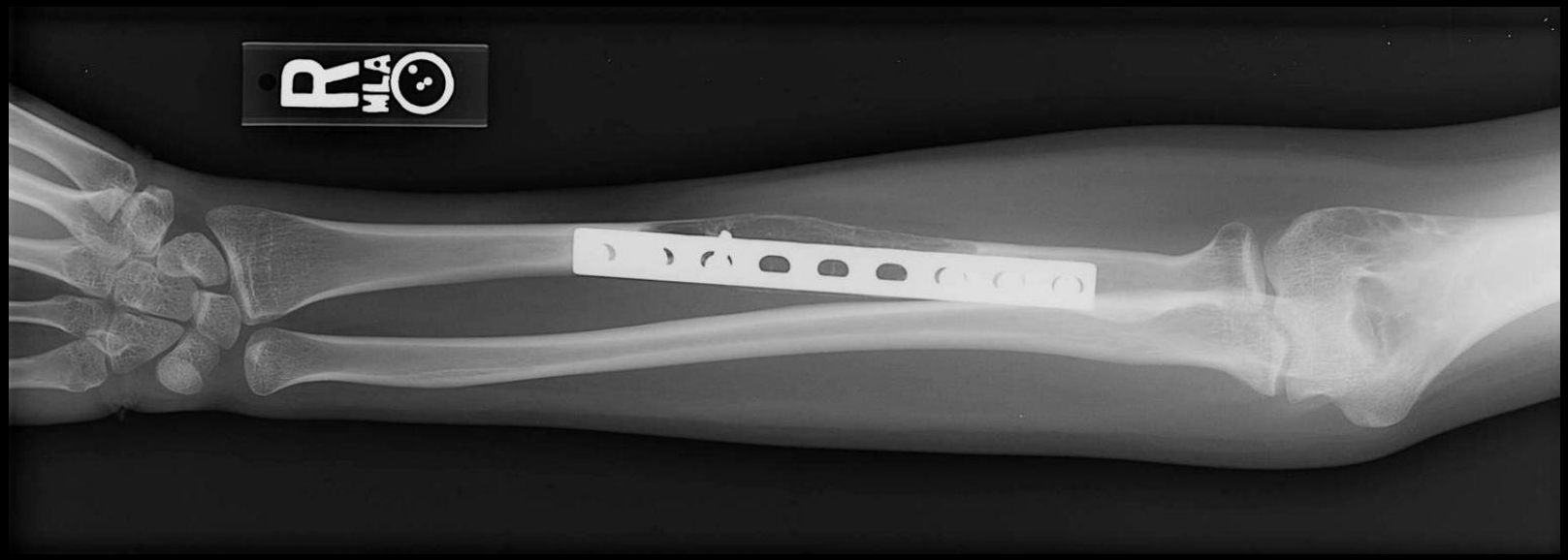
Bisphosphonate Fracture



Bisphosphonate Fracture Fixation



Prophylactic Fixation of Bone Lesion



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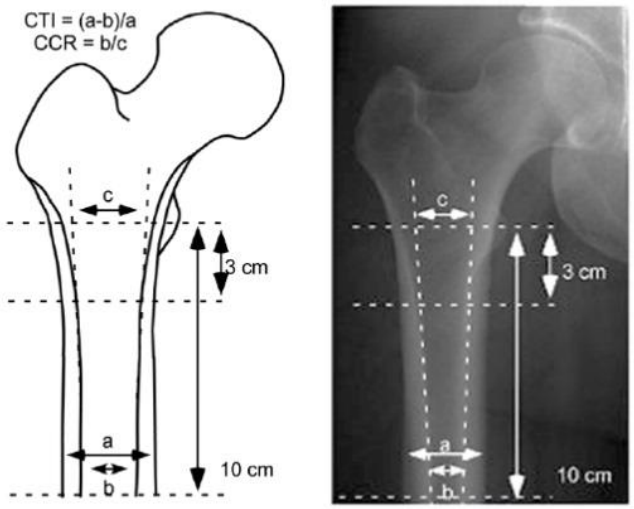
Research in LSD Bone Imaging

- New/modified imaging techniques to better characterize disease and progression
  - Alternatives to DEXA (bone cortical thickness, HR-pQCT)
  - MR spectroscopy for Gaucher disease
  - Artificial intelligence (AI) for image segmentation and interpretation

Radiographic Cortical Thickness

Radiographic Cortical Thickness Index Predicts Fragility Fracture in Gaucher Disease



CTI on a schematic (left) and radiograph (right).

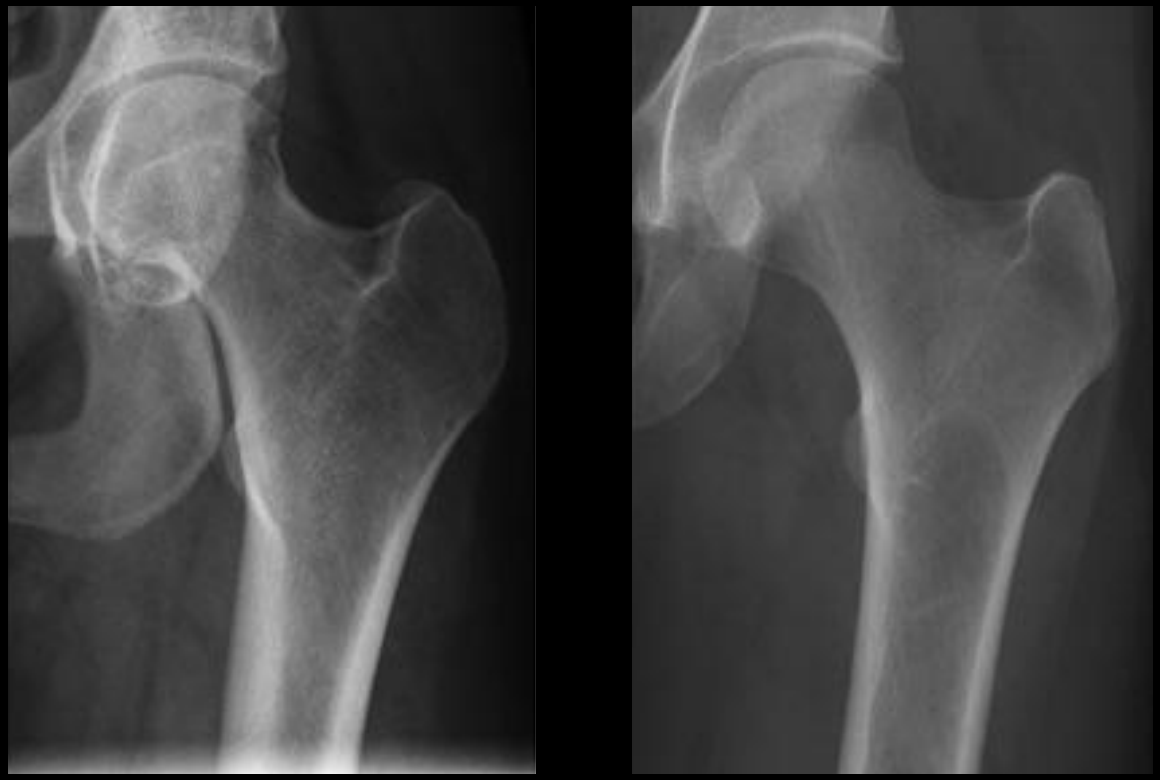
- Retrospective study in 247 patients with Gaucher disease with a median follow-up of 11 years (range, 2–30 years) showed femoral cortical thinning (cortical thickness index [CTI] ≤ 0.50) predicted fragility fractures (P = .01) independent of age, sex, fracture status, splenectomy, and delayed enzyme replacement therapy.
- CTI was a stronger predictor of future fracture (AUC, 0.96) than dual-energy x-ray absorptiometry, performed at various sites (T-score at total hip [AUC, 0.78], femoral neck [AUC, 0.73], forearm [AUC, 0.78], and spine [AUC, 0.69]).

D'Amore S et al. Published Online: December 20, 2022
https://doi.org/10.1148/radiol.212779

Radiology

From D'Amore *et al.*, *Radiology* 2023; 307:E212779.

Radiographic Cortical Thickness



From Hughes *et al.*, *J Bone Min Res*; 34:996-1013.

Radiographic Cortical Thickness

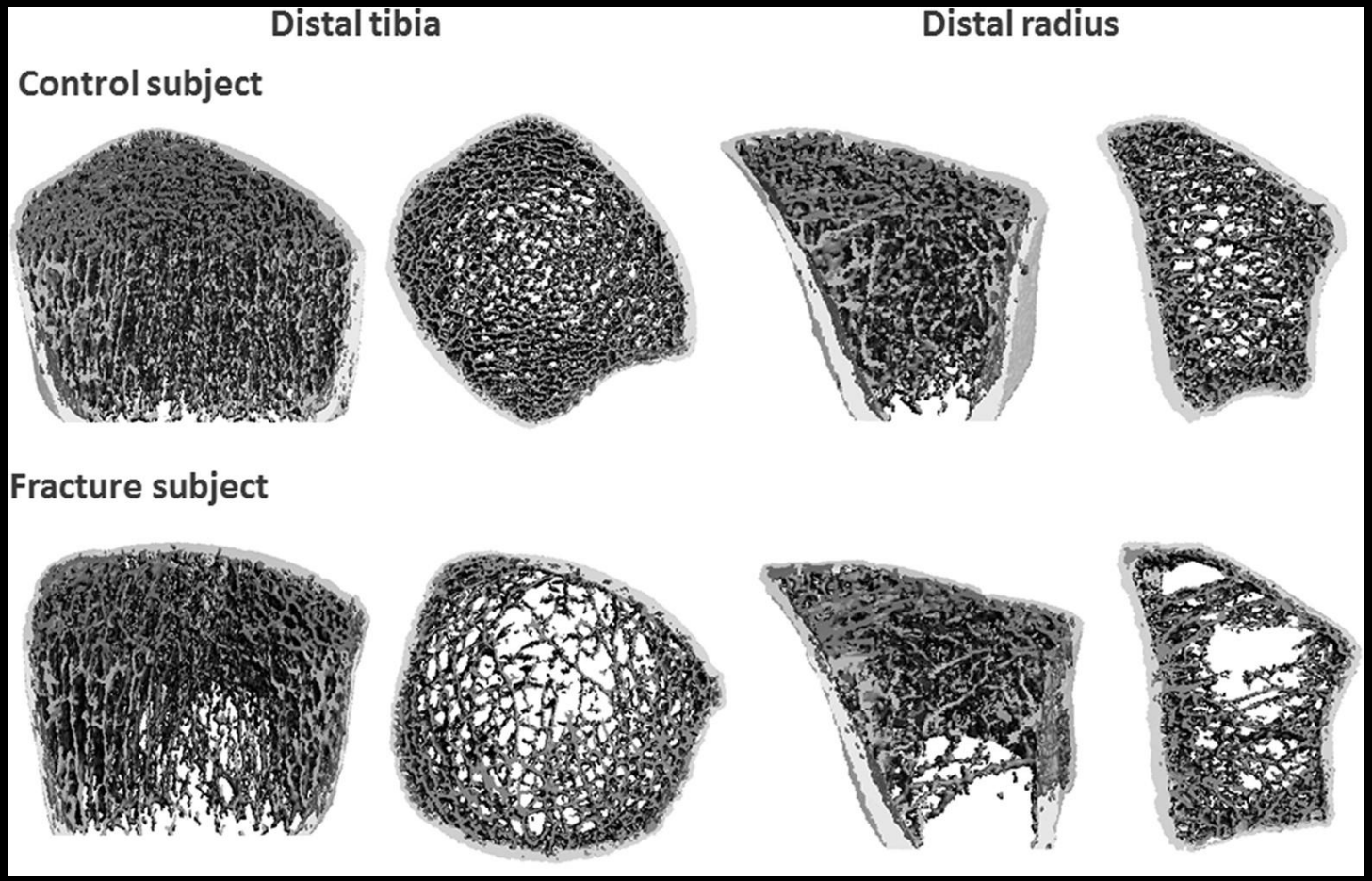
- Radiographic cortical thickness can provide information without requiring an additional test of piece of equipment
- Potentially useful in resource-poor areas
- Amenable to analysis by artificial intelligence (AI) and machine learning algorithms

High-Resolution Peripheral QCT

- HR-pQCT uses non-invasive, in vivo imaging of the distal radius and distal tibia to provide volumetric measurement of BMD and 3D assessment of bone microarchitecture
- Can examine structural properties and geometry of cortical and trabecular bone
- Higher sensitivity for detecting skeletal changes as compared to DEXA, including over shorter time intervals

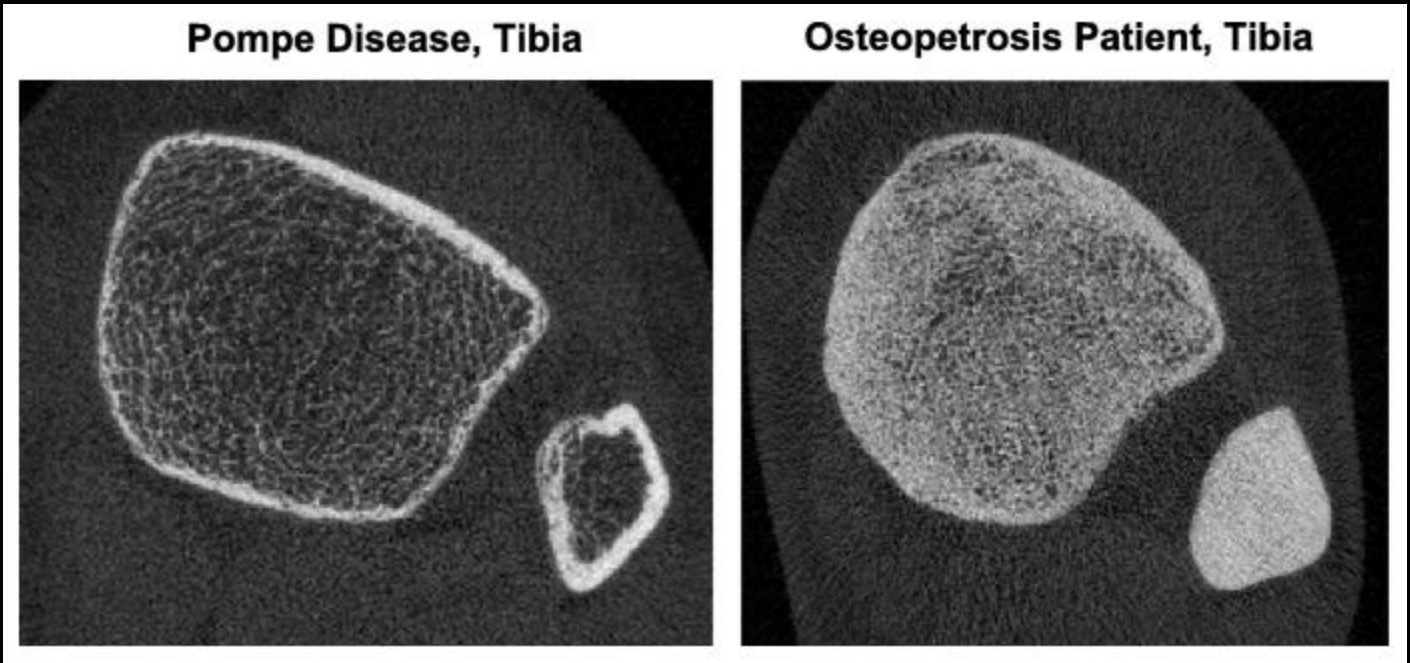
From https://www.monash.edu/medicine/scs/research/bone-muscle/clinical-imaging-service/hr-pqct

High-Resolution Peripheral QCT



From Zhu *et al*. *Scientific Reports* 2016; 6: 34185.

High-Resolution Peripheral QCT



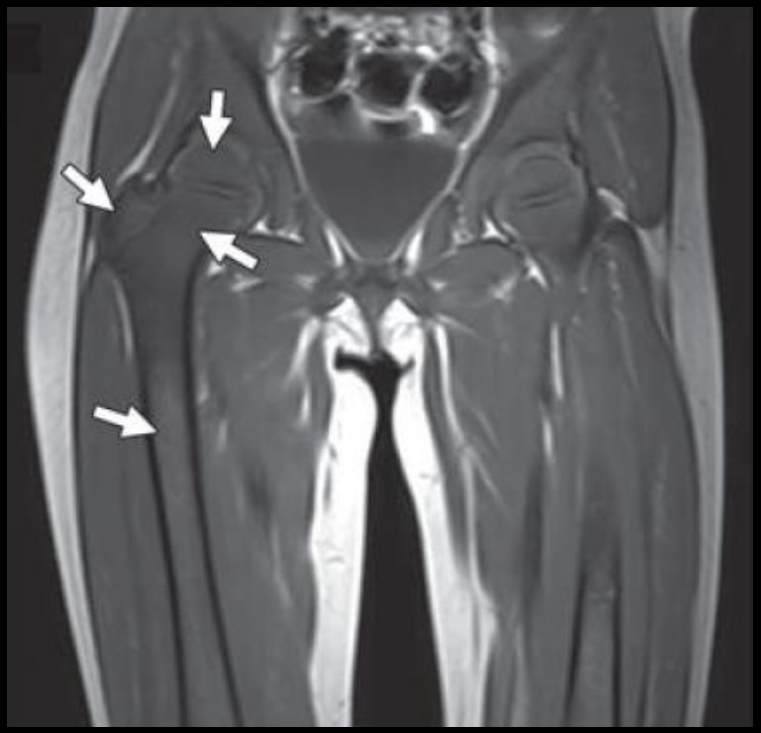
From Sidhu *et al*. *Orphanet J Rare Dis* 2020; 15: 251.

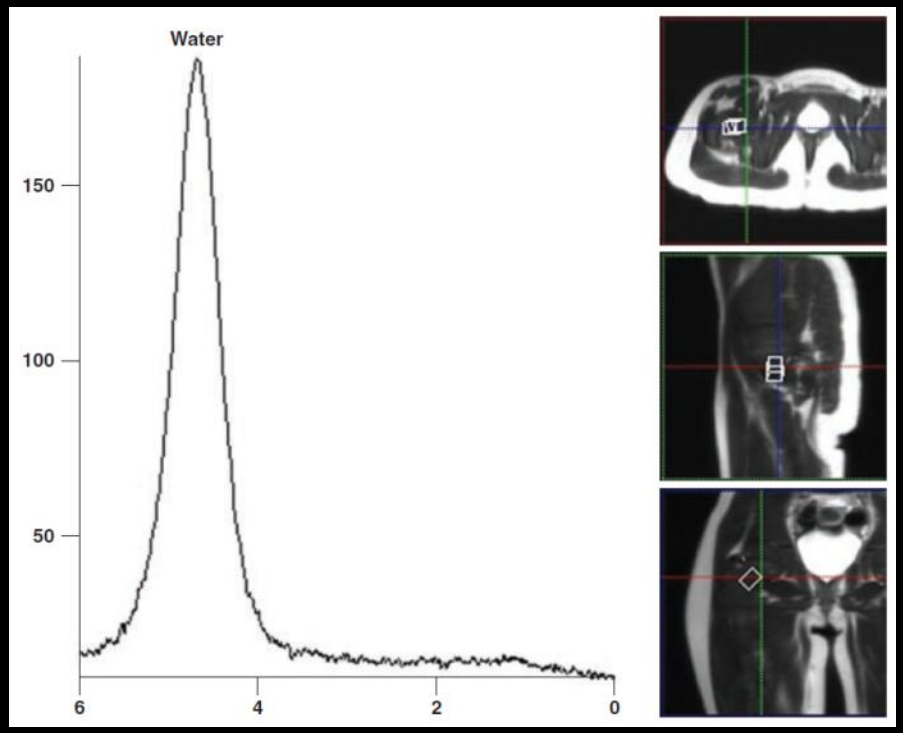
Proton MR Spectroscopy

- Difficult to differentiate dark marrow from hematopoietic red marrow in young patients, especially children
- Physiologic process of red marrow conversion during development further confounds assessment
- MRS provides a direct quantitative measurement of the chemical composition of the bone marrow (fat fraction)

Proton MR Spectroscopy

6-year old girl with GD, untreated

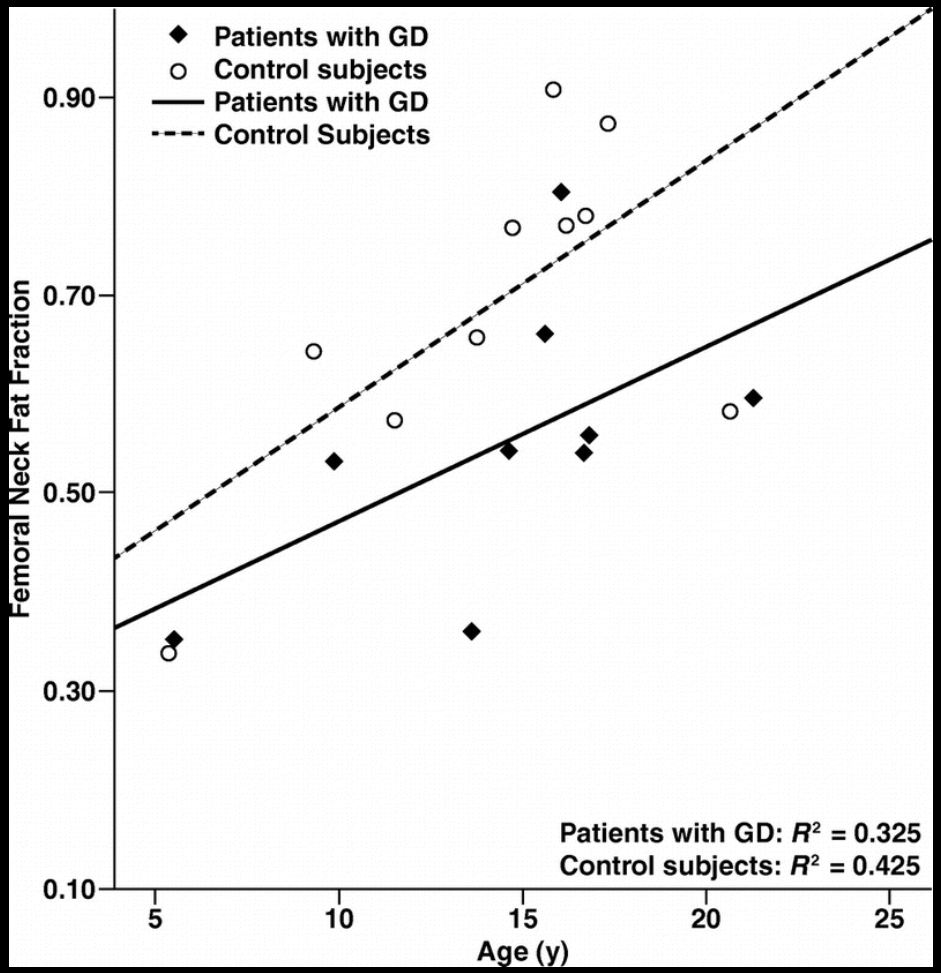




Femoral neck FF < 0.01

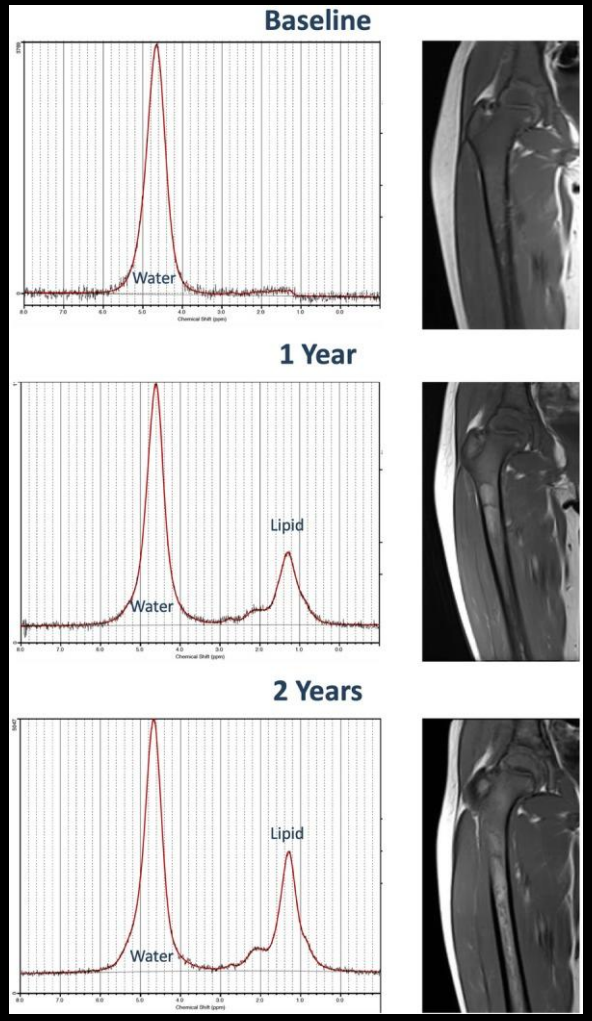
From Jaramillo *et al*. *AJR 2015*; 204: 1296-1302.

Proton MR Spectroscopy



From Jaramillo *et al*. *AJR 2015*; 204: 1296-1302.

Proton MR Spectroscopy



15 years

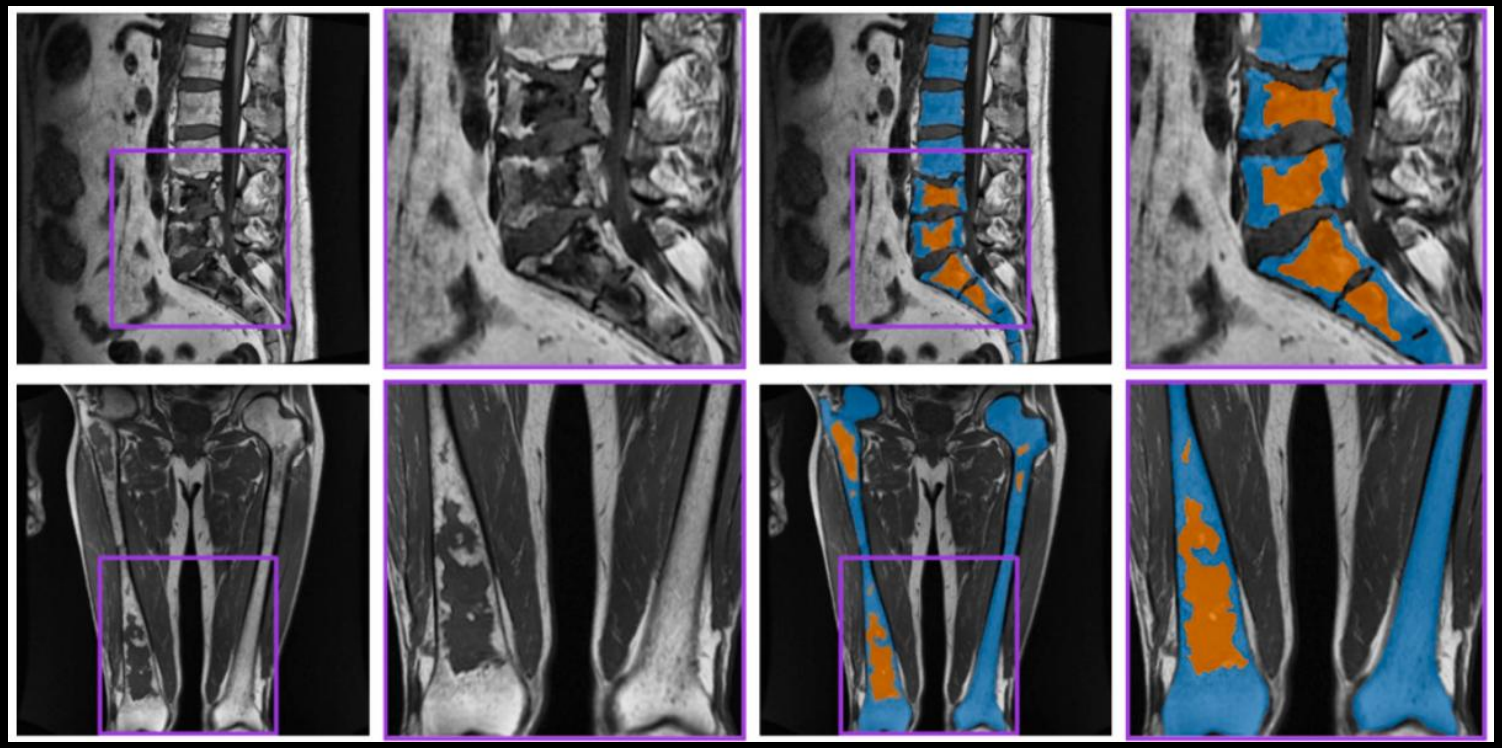
From Degnan *et al*. *Insights Imaging 2019*; 10: 70.

Proton MR Spectroscopy

- Proton MRS can quantify marrow burden in pediatric GD when MRI shows no qualitative difference from controls, even when GD patients are/have been on ERT
- Normal marrow conversion can affect results (expected increase in FF with age)
- Need a larger study – a prospective longitudinal controlled study of patients with GD from initiation of ERT or SRT

AI/Deep Learning for MRI

- Deep learning-based quantification for the segmentation of osteonecrosis on MRI images of the lumbar spine and femur



From Yu *et al*. *Bone* 2024; 186: 1-11.

AI/Deep Learning for MRI

- Many potential uses, including improved standardization of MRI image interpretation, bone scoring, and evaluation of bone architecture
- Can use to quantify size of bone lesions
- First step in automation of MRI scoring, in order to identify bone lesions to exclude from ‘background’ bone marrow

Outline

- Introduction to lysosomal storage disorders (LSDs)
- Imaging of skeletal abnormalities in LSDs
  - MPS (dysostosis multiplex)
  - Pyknodysostosis
  - Gaucher disease
- Management of bone abnormalities in LSDs
  - Role of the orthopedic surgeon
- Recent developments
- Q&A

Bone Complications in Lysosomal Storage Disorders

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