RADY 403 Case Presentation

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UNC SCHOOL OF MEDICINE
Radiology

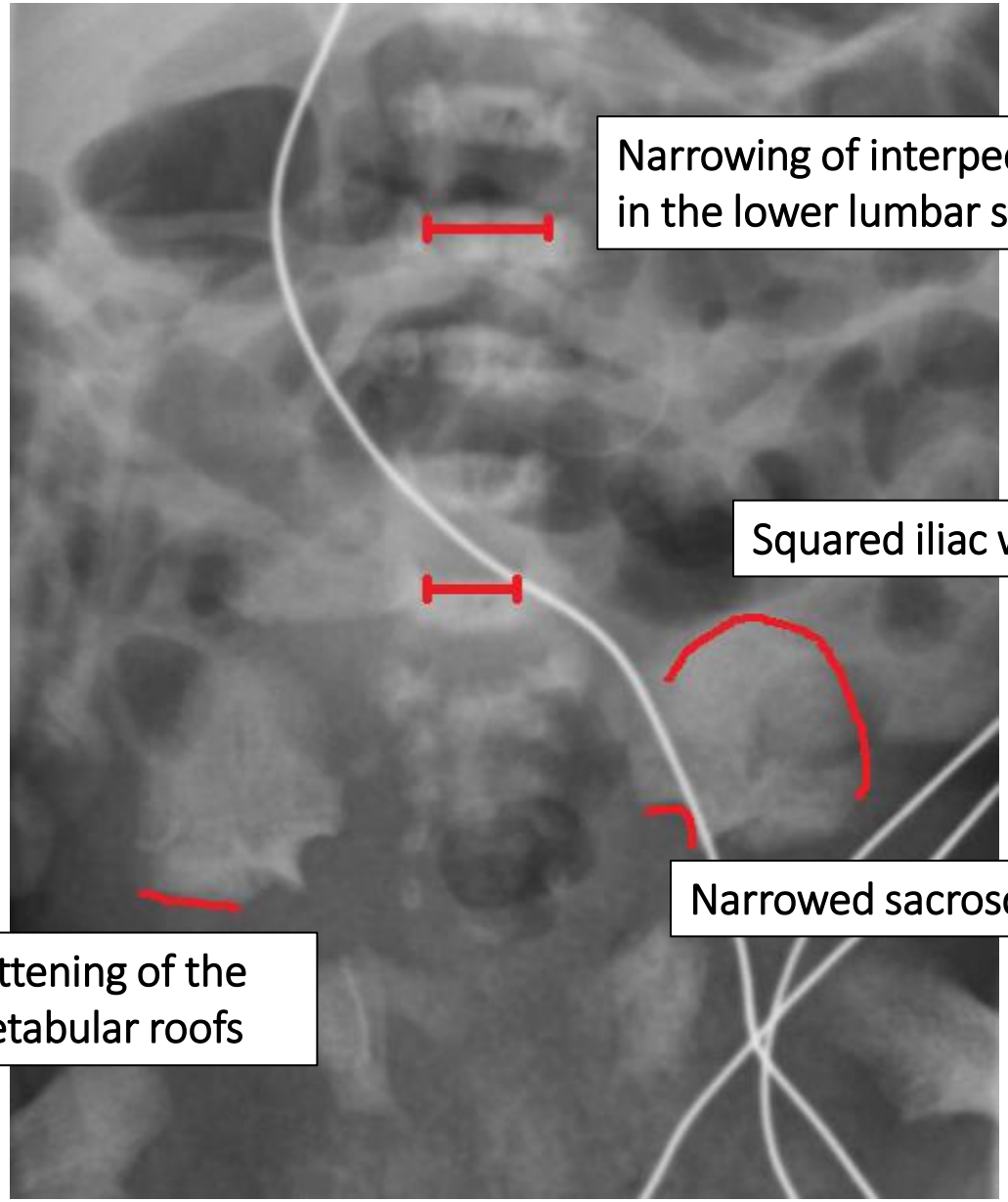
Focused patient history and workup

- Neonate male born at 34 weeks via pre-term spontaneous vaginal delivery to a now G2P0202 mother. APGARs 4 and 7. Required PPV, CPAP, and O2 at delivery. Admitted to NICU for management of respiratory distress.
- Pregnancy otherwise complicated by skeletal dysplasia and mild polyhydramnios. Mother declined amniocentesis for further workup.
- PE: head slightly enlarged compared to body with prominent forehead, shortened limbs, narrow torso with equal air entry and chest excursion
- DDx: achondroplasia vs. osteogenesis imperfecta
- Karyotype: 46XY
- Microarray: normal male microarray result
- **Skeletal dysplasia panel: mutation detected in the FGFR3 gene**

List of imaging studies

- Skeletal survey at birth
- CT head at 8 months
- MRI brain at 8 months, 9 months, and 17 months
- X-ray scoliosis AP and lateral at 2 years and 2y1m
- X-ray abdomen at 2y5m

Skeletal survey at second day of life



Narrowing of interpedicular distance in the lower lumbar spine

Squared iliac wings

Narrowed sacrosciatic notches

Flattening of the acetabular roofs

X-ray from a patient without achondroplasia for comparison

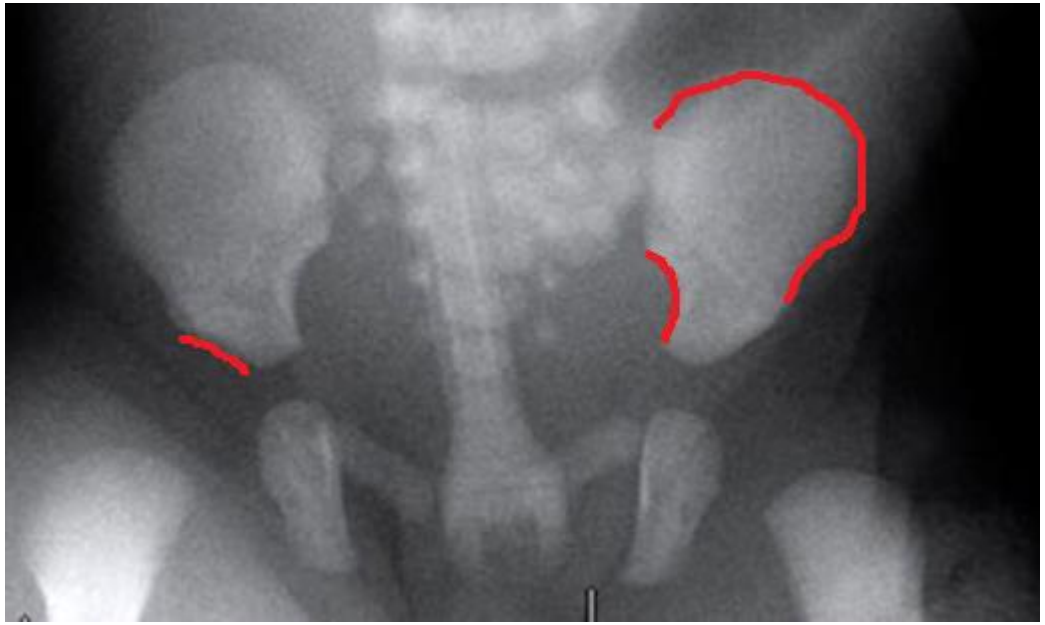
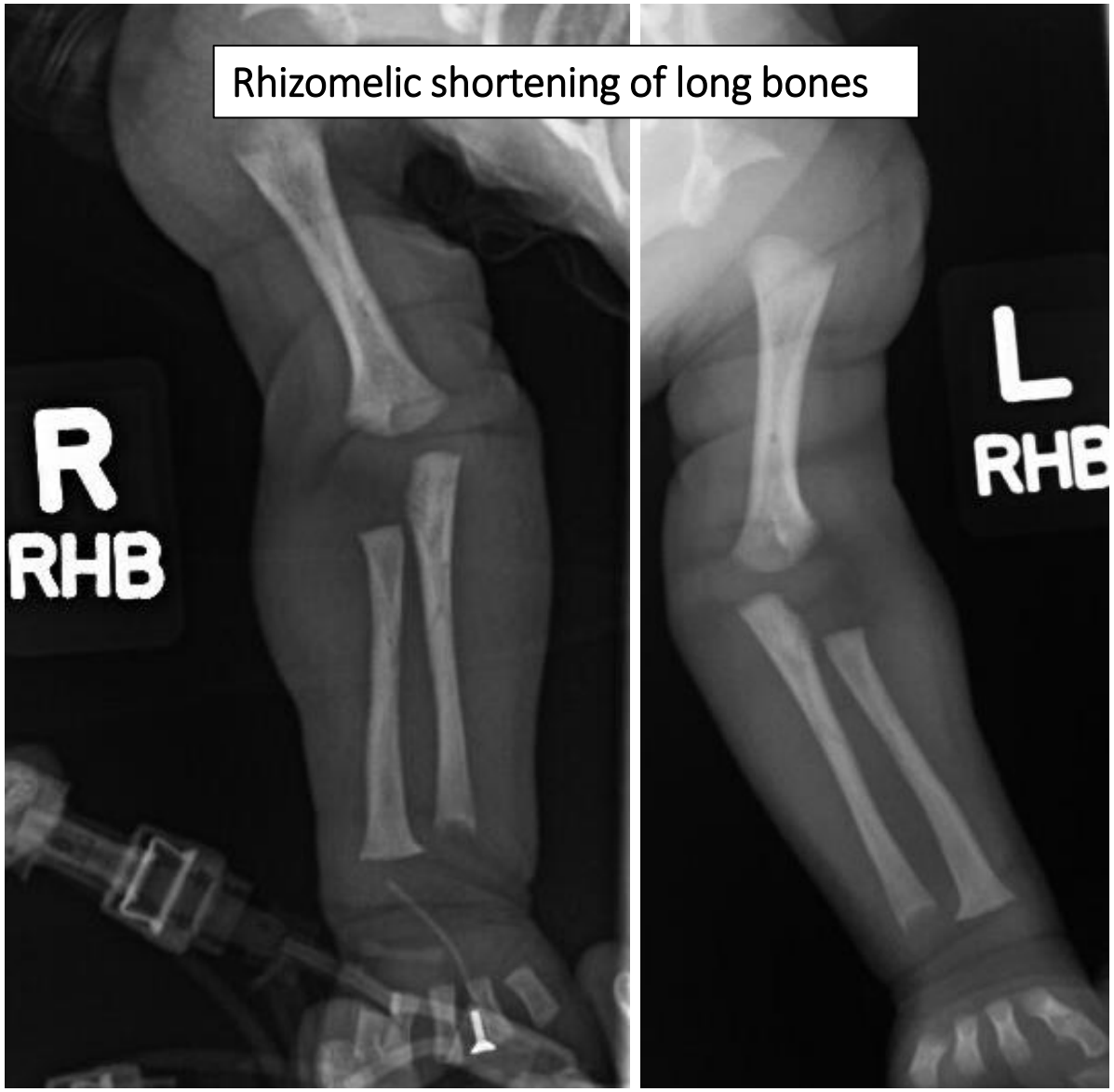
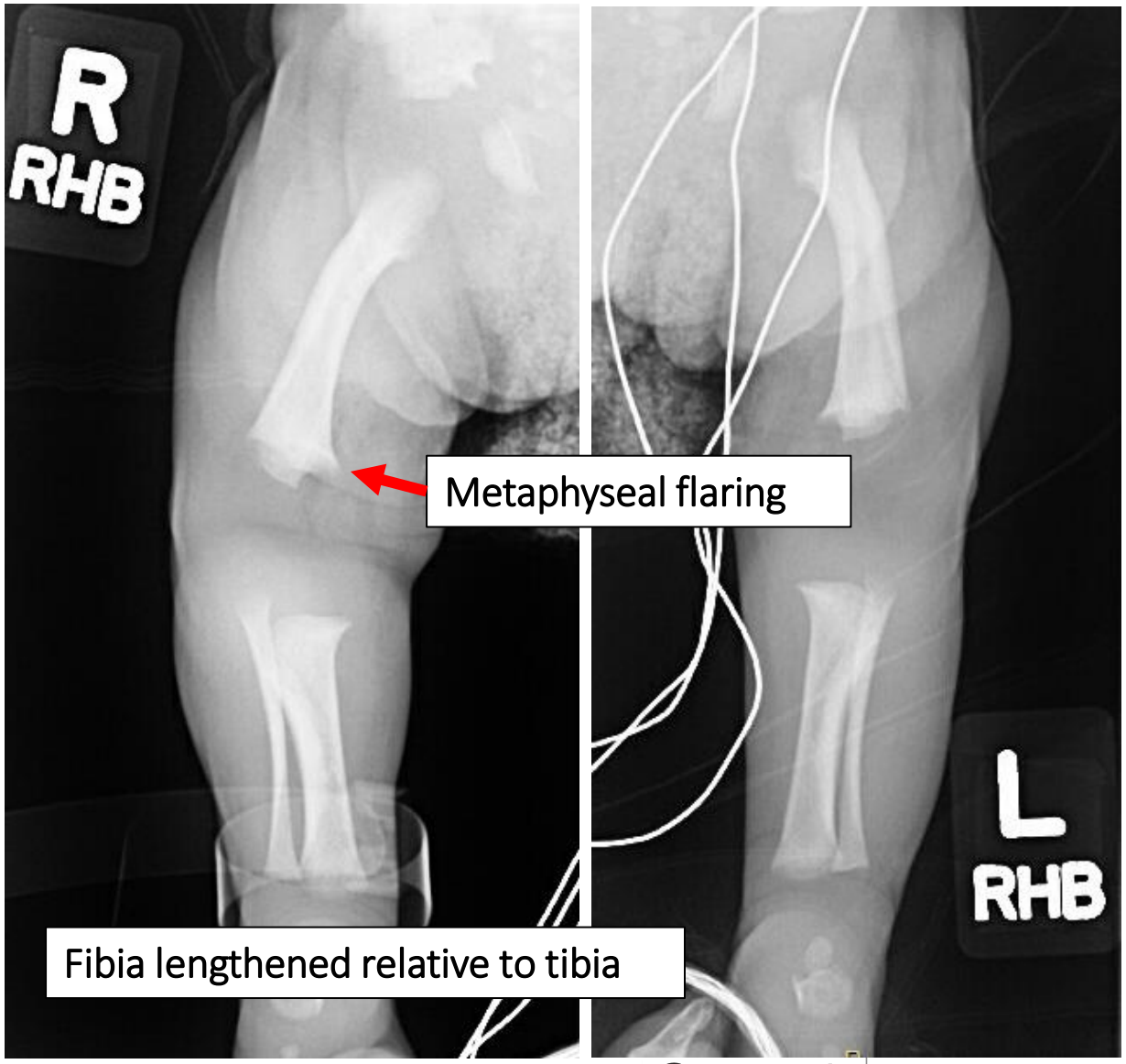


Image from https://radiologyassistant.nl/pediatrics/acute-abdomen/acute-abdomen-in-neonates

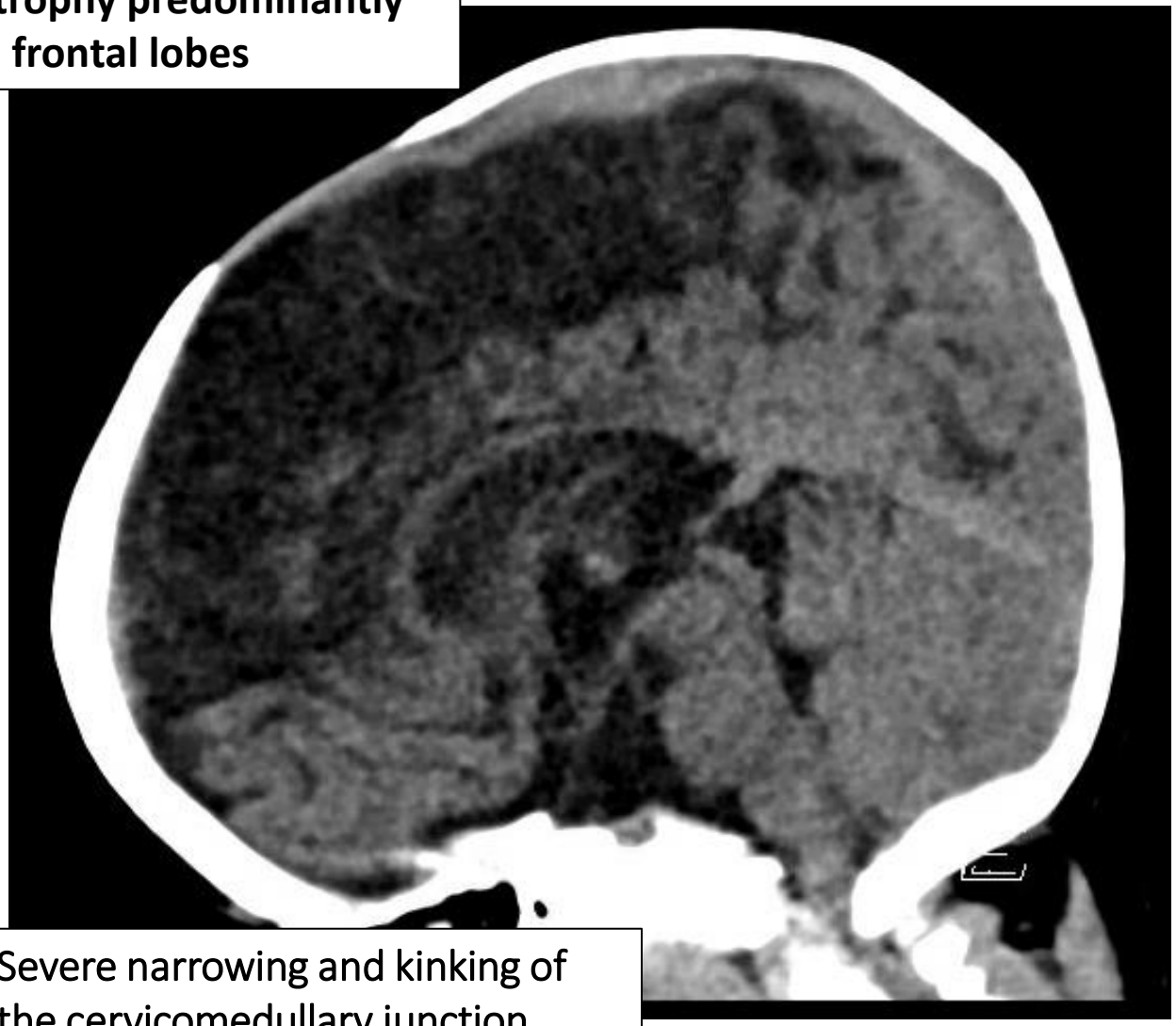
Skeletal survey at second day of life



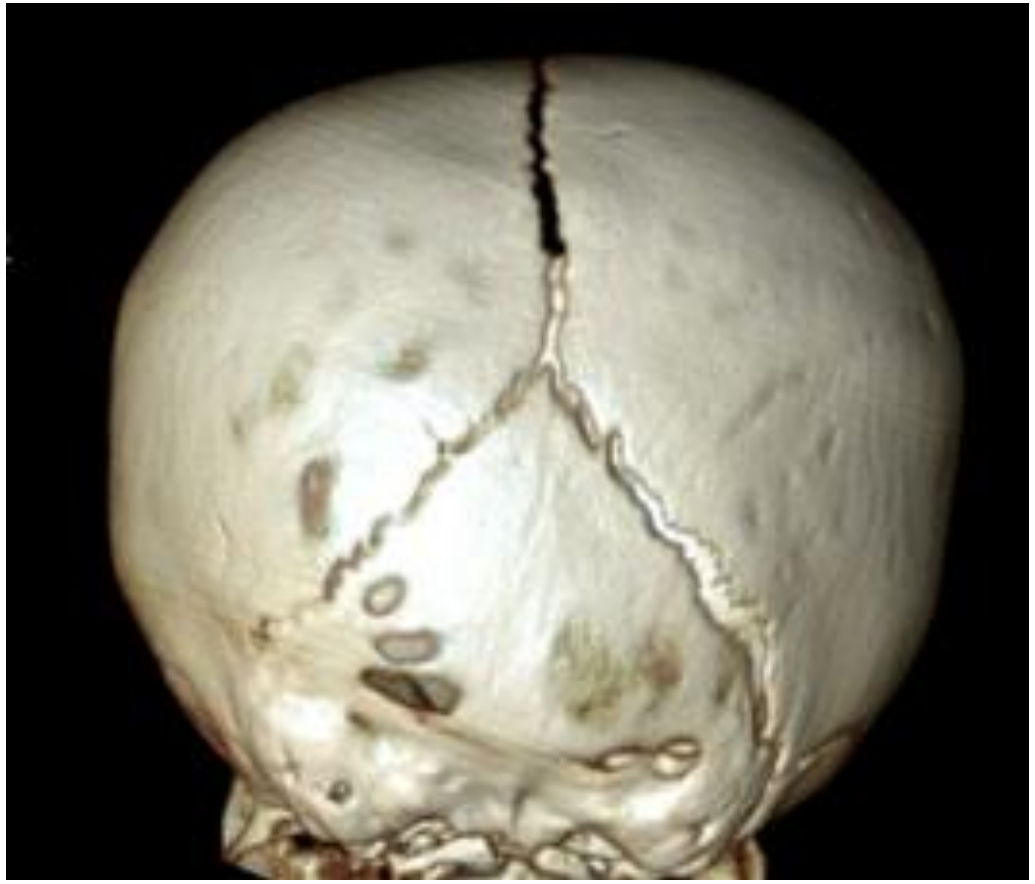


CT head at 8 months

Atrophy predominantly in frontal lobes

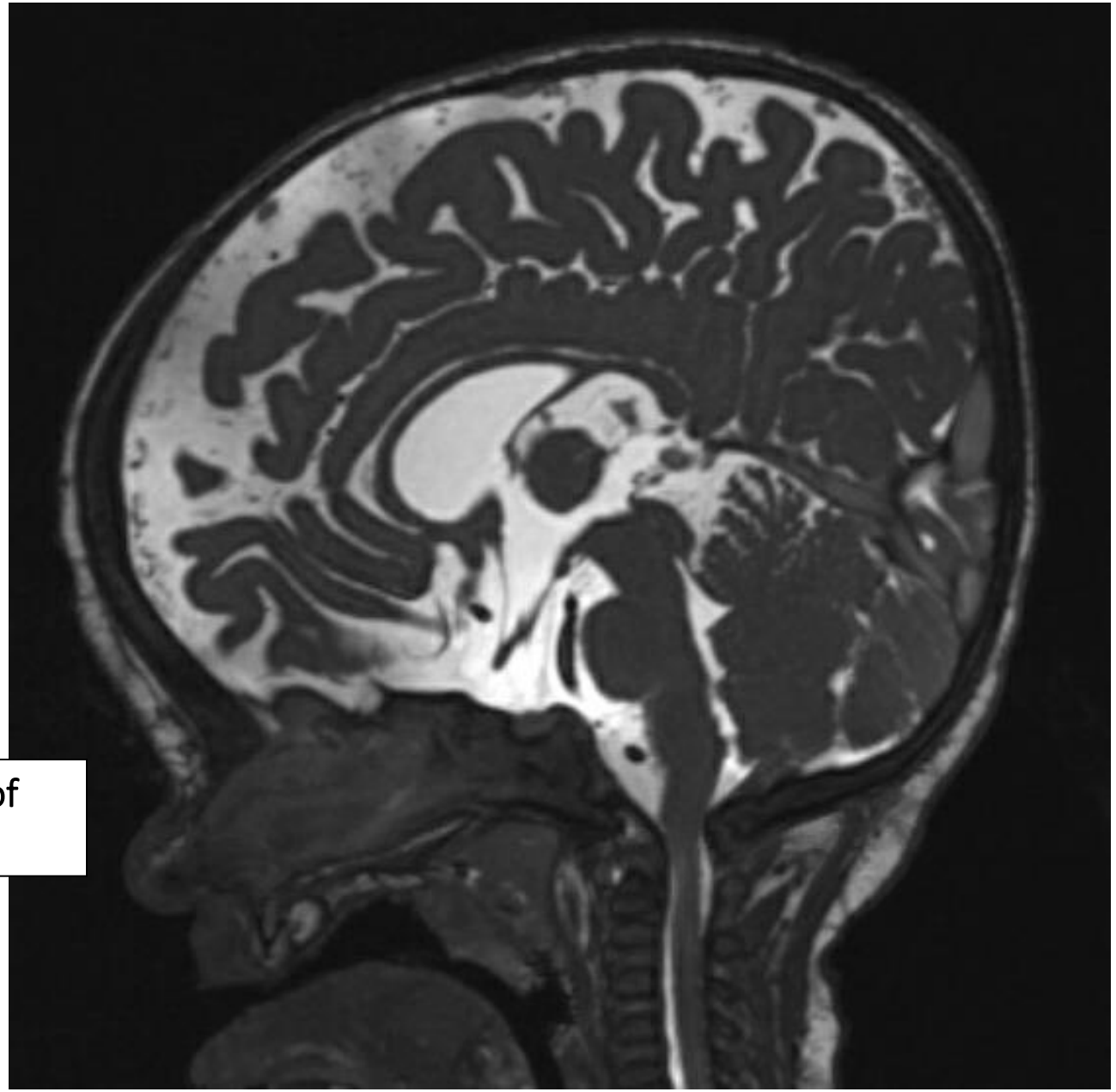


Severe narrowing and kinking of the cervicomedullary junction



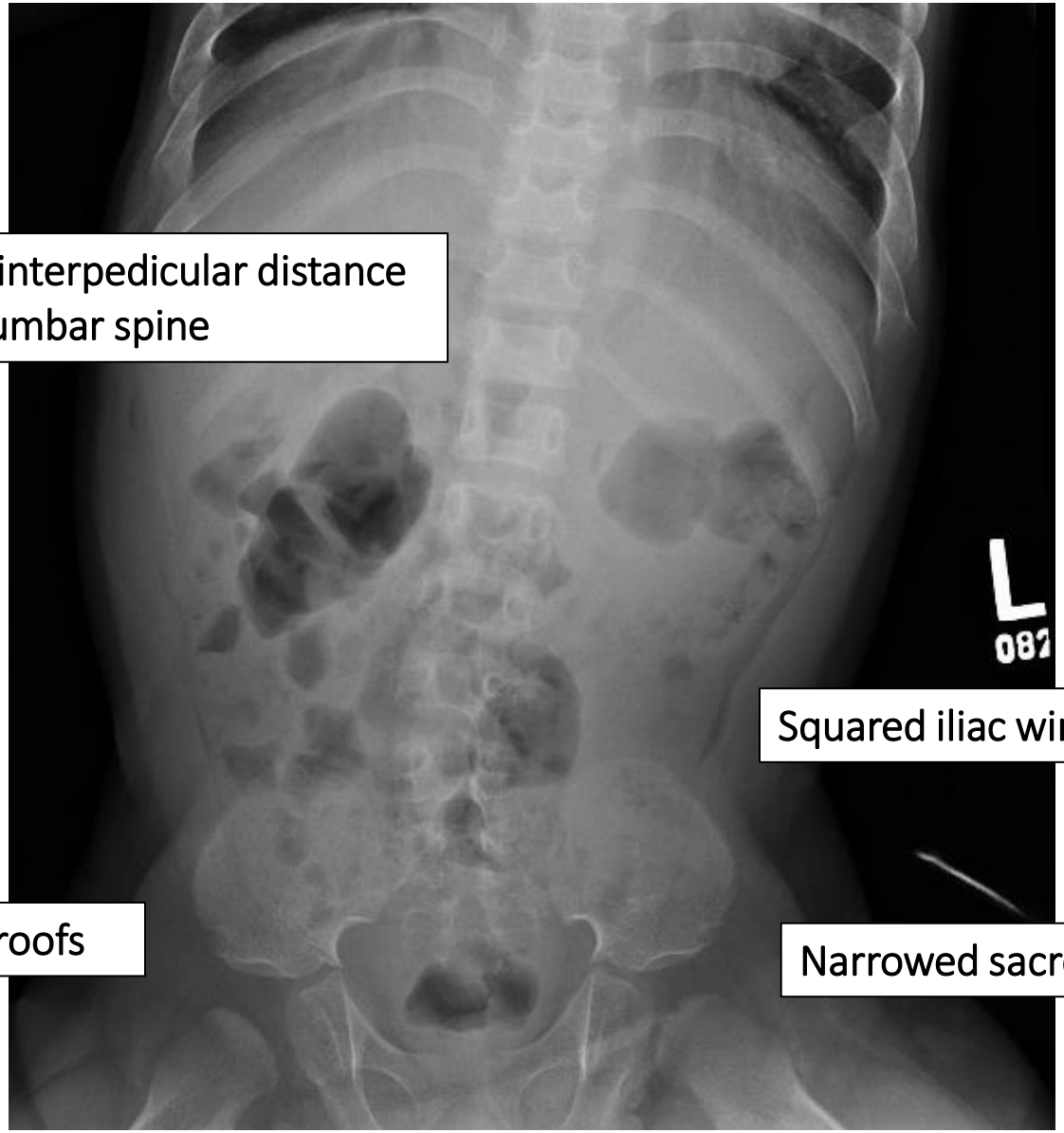
Plagiocephaly and fusion of left lambdoid and squamousal sutures

MRI brain at 8 months



Severe narrowing and kinking of the cervicomedullary junction

Abdominal X-ray at 2y5m



Narrowing of interpedicular distance in the lower lumbar spine

Squared iliac wings

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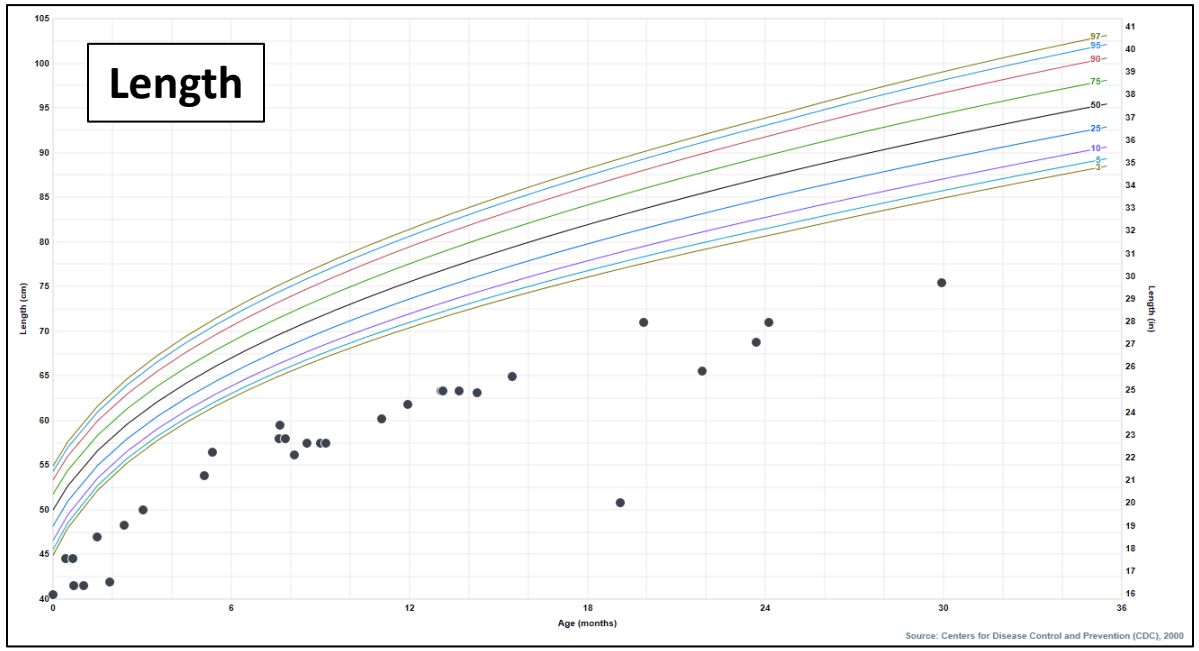
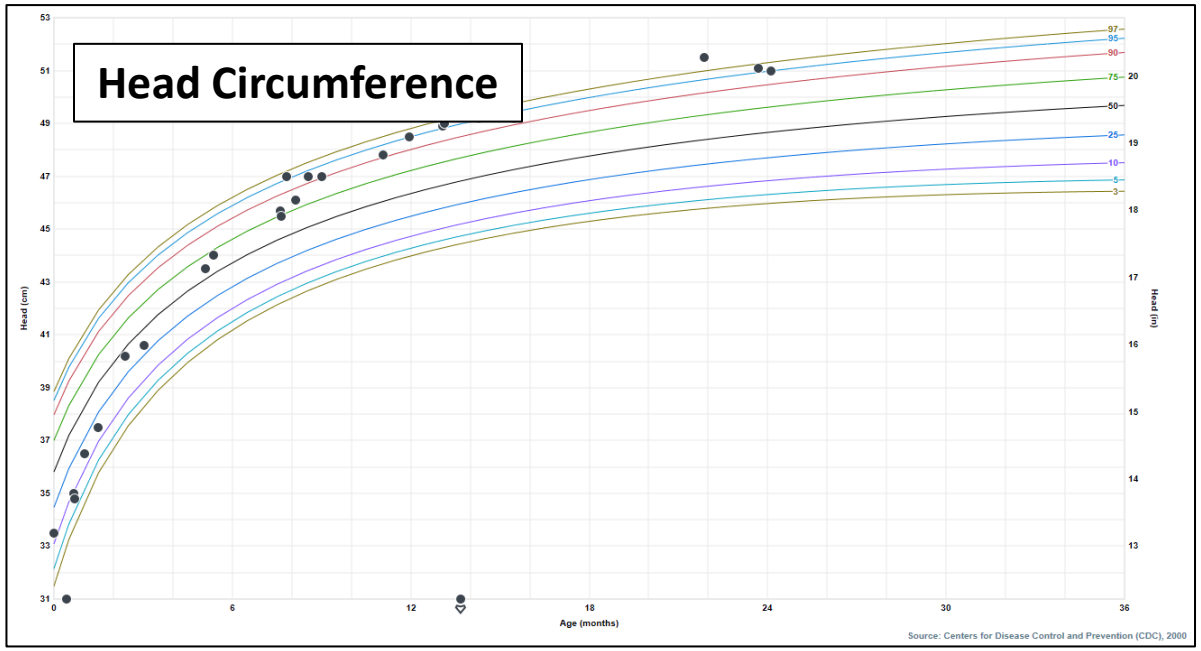
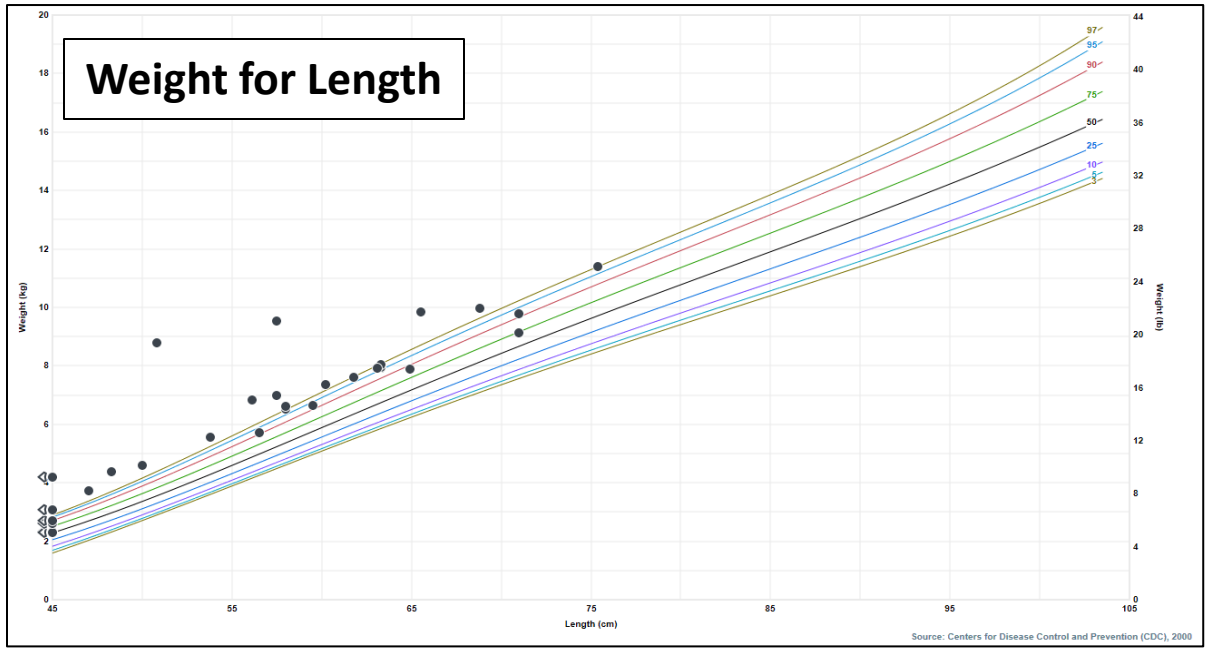
Narrowed sacrosciatic notches

Patient treatment and outcome

- Head US with grade I IVH in L lateral ventricle, MRI later with evidence of L caudothalamic groove hemorrhage
- In NICU, had repeated episodes of apnea/bradycardia/desaturation that resolved with stimulation and head repositioning
- Discharged on day of life 48 with low flow O2

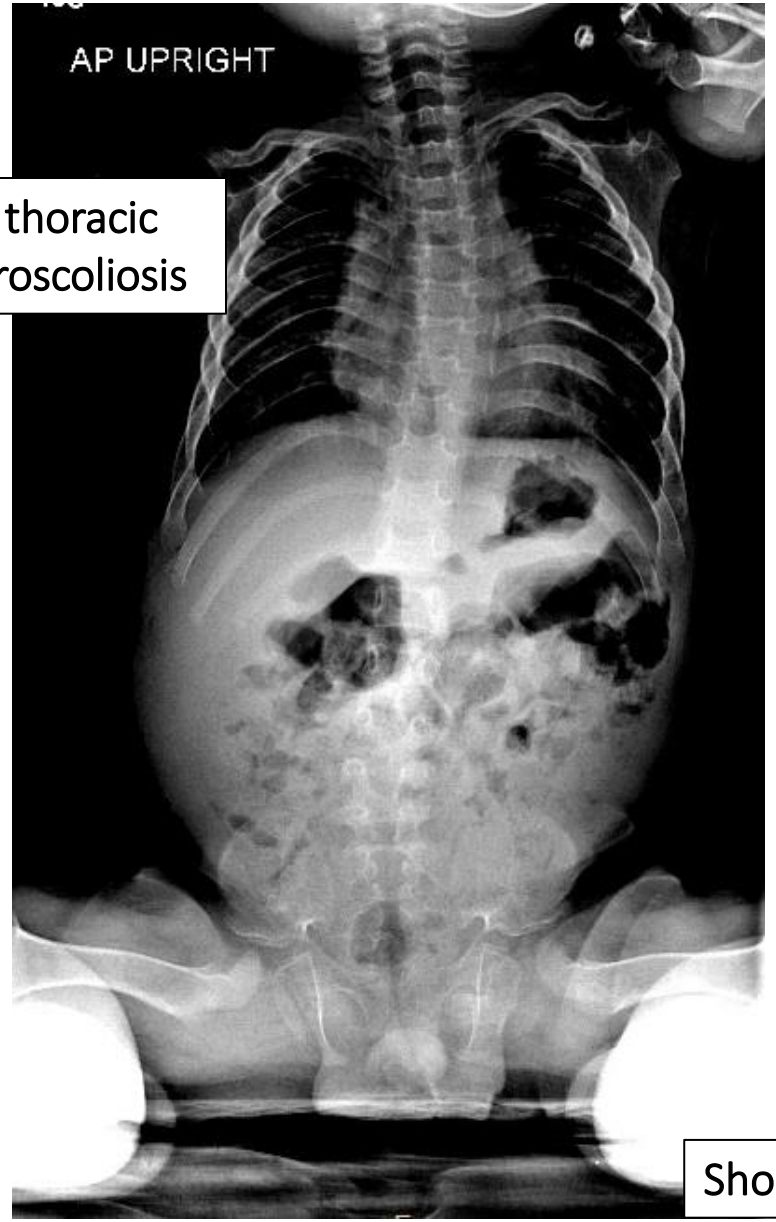




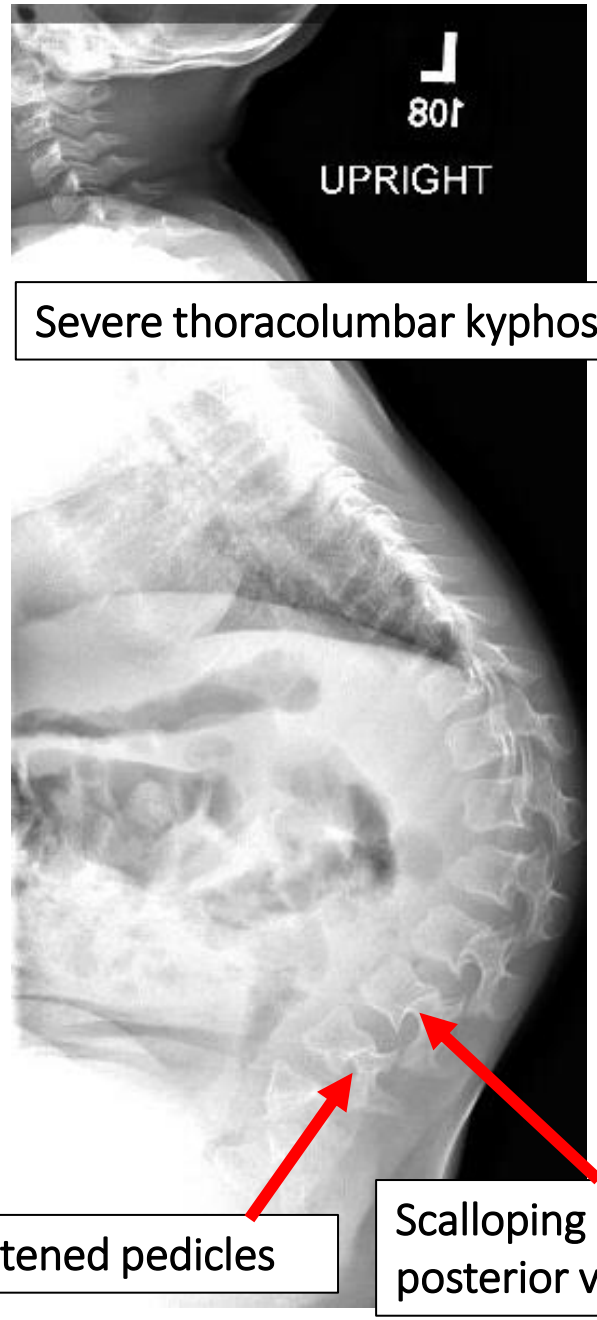


- Short stature
- Severe global developmental delay—at 2.5 years old, not yet walking and nonverbal
- Worsening kyphoscoliosis—followed by orthopedics who started back brace in February 2020

X-ray scoliosis at 2 years



Mild thoracic dextroscoliosis

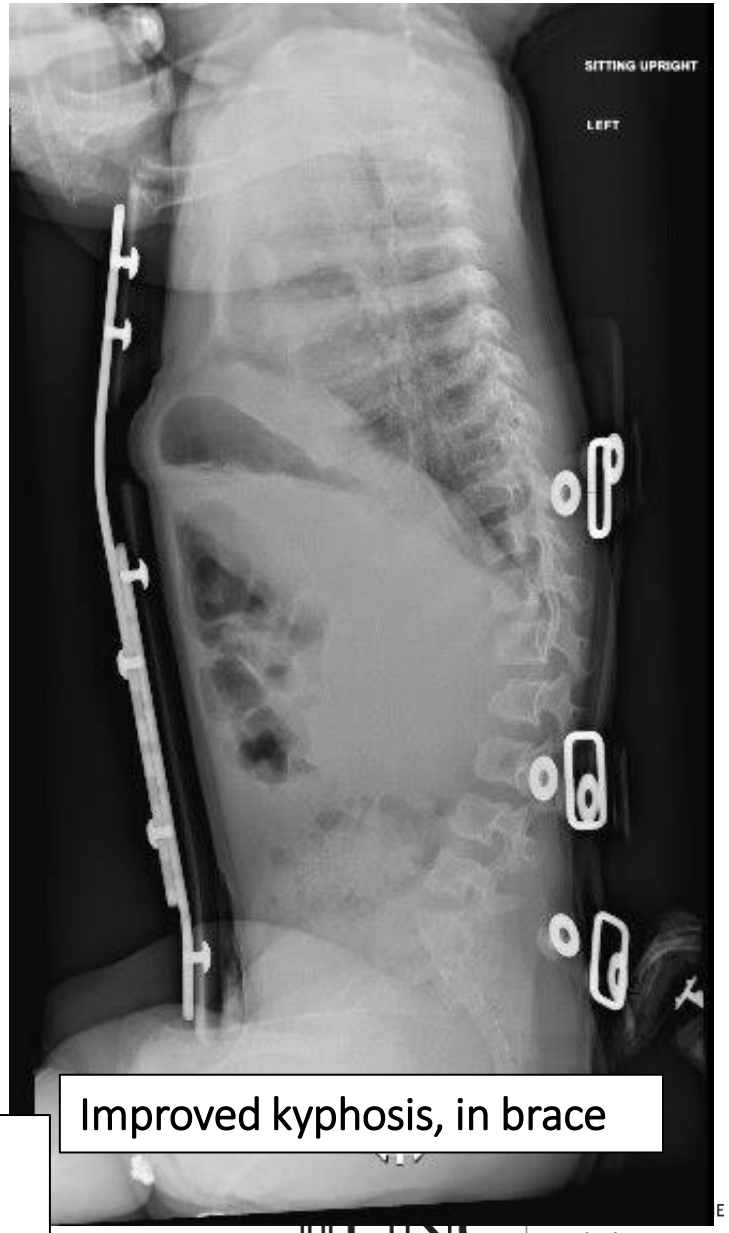


Severe thoracolumbar kyphosis

Shortened pedicles

Scalloping of posterior vertebrae

F/u film 1 month later



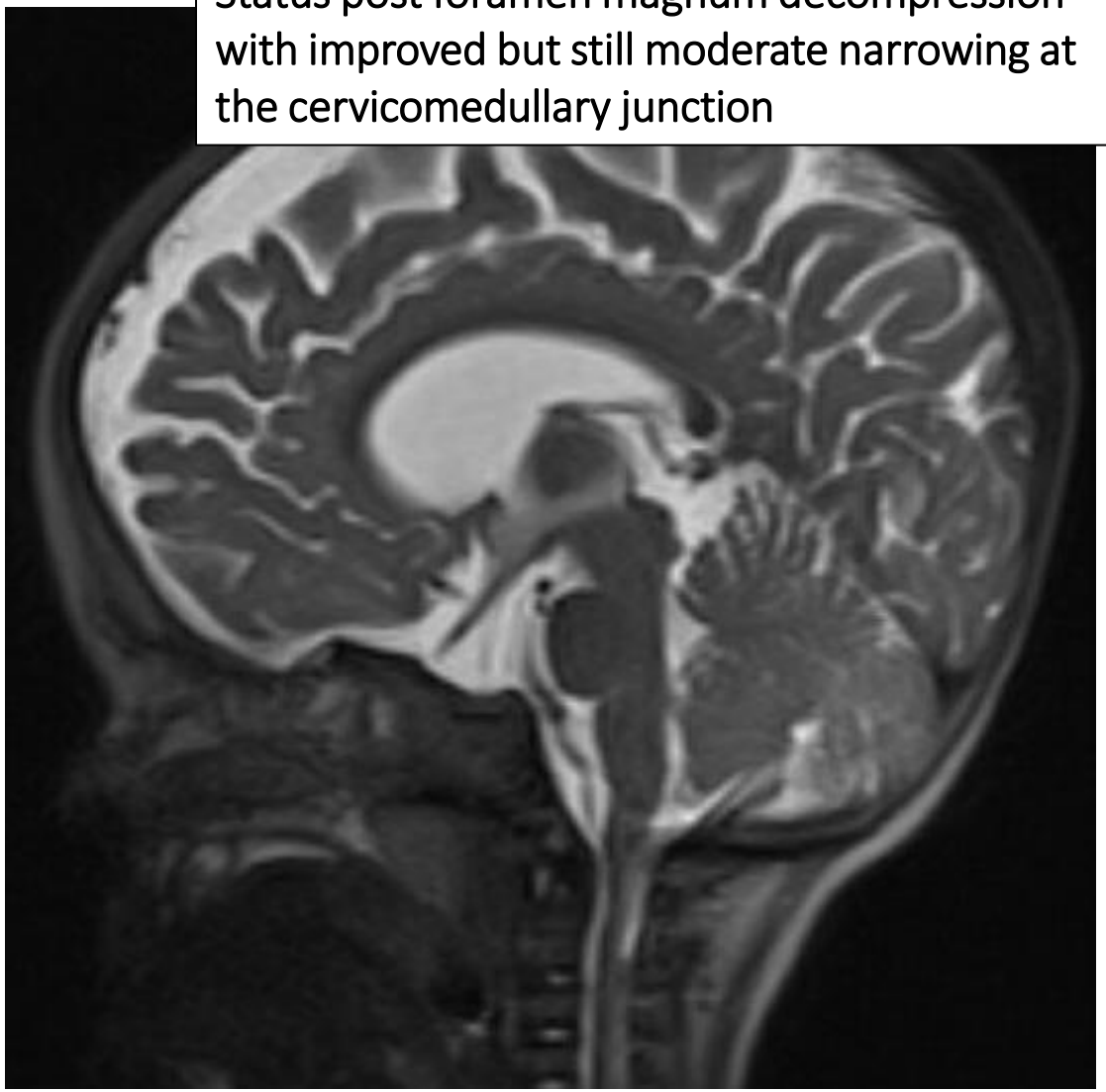
Improved kyphosis, in brace

Patient treatment and outcome

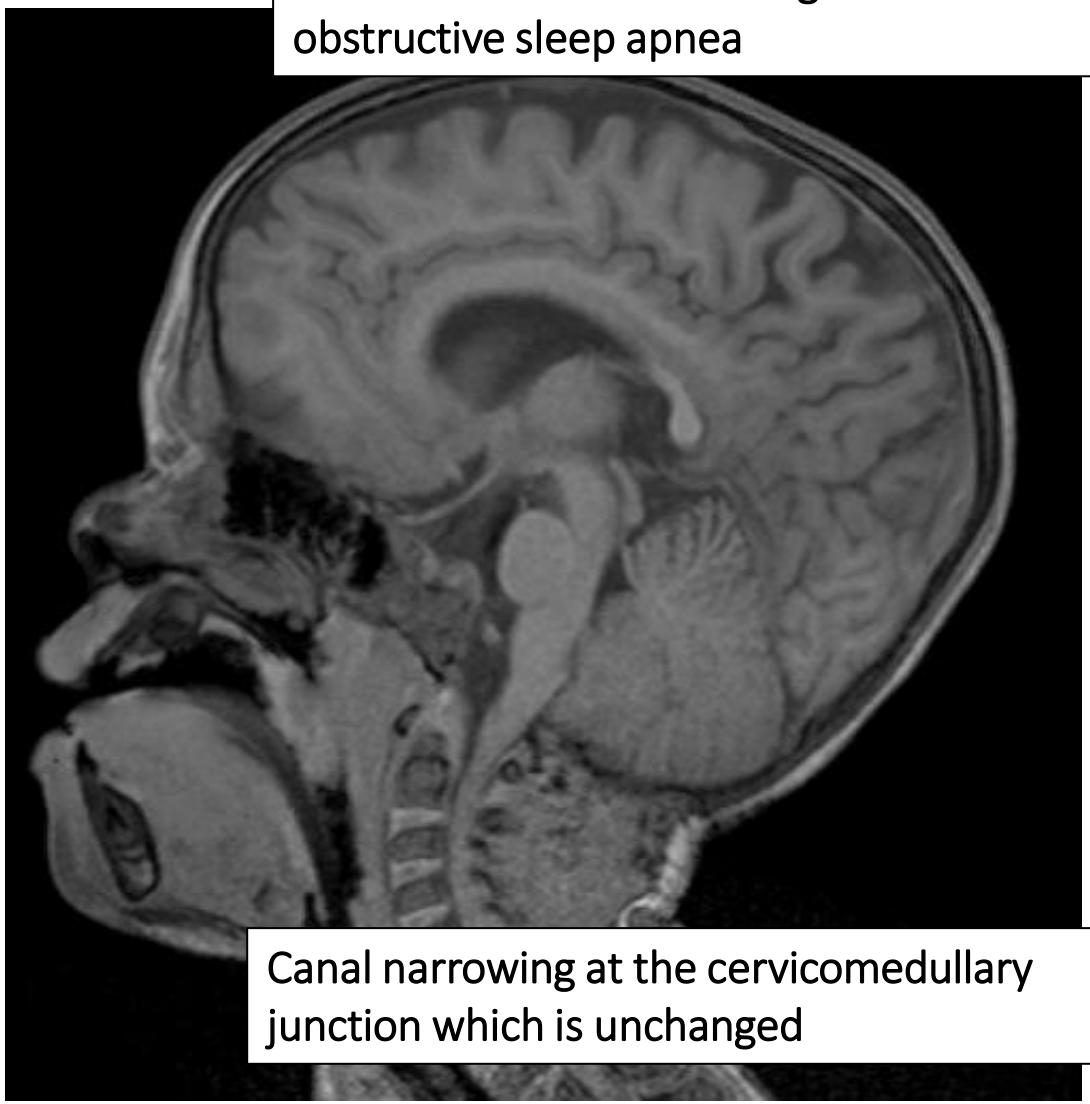
- Severe obstructive and central sleep apnea as well as daytime desaturations
  - Multiple episodes of apnea requiring CPR
- Foramen magnum decompression surgery in October 2018
- Tonsillectomy and adenoidectomy in July 2019
- Despite these interventions, most recent sleep study in July 2020 with worsened OSA and central sleep apnea

MRI brain at 9 months and 17 months

Status post foramen magnum decompression with improved but still moderate narrowing at the cervicomedullary junction



MRI obtained for worsening central and obstructive sleep apnea



Canal narrowing at the cervicomedullary junction which is unchanged

Patient treatment and outcome

- Followed by a number of other specialists besides genetics, orthopedics, and pulmonology as previously described
  - ENT—recurrent ear infections and URIs, bilateral tympanostomy rubes
  - Ophthalmology—R esotropia, R amblyopia
  - Gastroenterology—persistent vomiting
  - Feeding team
  - OT
  - PT
  - SLT
  - SICC
- Considering the developmental delay and severe apnea, some physicians raised the question of SADDAN (Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans)

Discussion: etiology

- Achondroplasia is the most common bone dysplasia, with prevalence of ~1 in 20,000 live births
- Caused by AD gain-of-function mutation in FGFR3, leading to permanent activation which inhibits chondrocyte proliferation[1]
  - 80% are de novo mutations
  - Associated with advanced paternal age[2]
- Phase 3 trial of **vosoritide**, a recombinant CNP with greater half-life, demonstrated 1.57cm per year greater growth (95% CI 1.22, 1.93)[3]

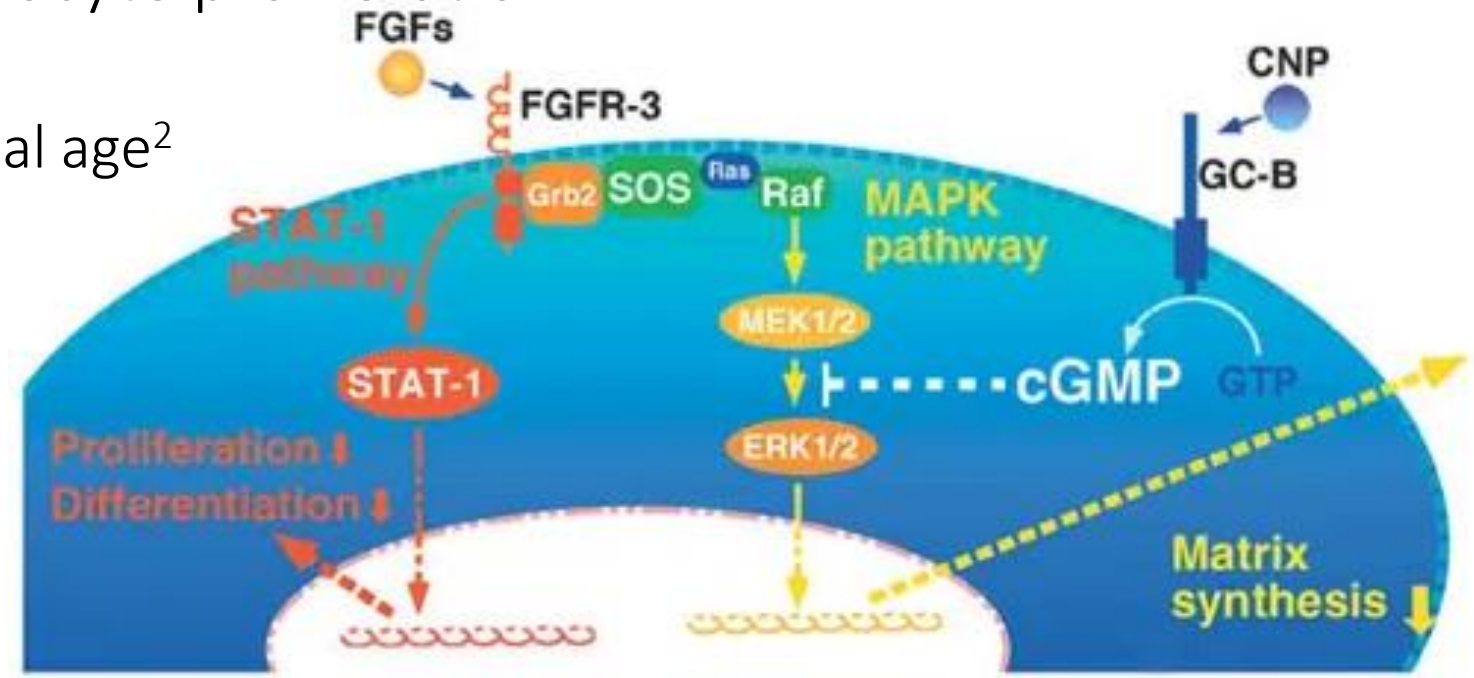


Image from Yasoda, A., Komatsu, Y., Chusho, H. *et al.* Overexpression of CNP in chondrocytes rescues achondroplasia through a MAPK-dependent pathway. *Nat Med* **10,** 80–86 (2004). https://doi.org/10.1038/nm971

Discussion: clinical findings

- Short stature with rhizomelia, brachydactyly with tridentine appearance, kyphoscoliosis, and lumbar lordosis
  - Kyphosis improves and lordosis worsens after ambulation begins
- Macrocephaly with frontal bossing, midface hypoplasia, saddle nose deformity
- Slow motor development, resolving by age 2-3
  - Due to joint laxity and disproportionate head[4]
- Normal intellectual development
- Normal expected lifespan

Photo from https://sites.google.com/site/lesscommon diagnosessyndromes/achondroplasia

Discussion: complications

- Recurrent otitis media—due narrowed auditory canal
- Obstructive sleep apnea—due to facial changes
- Leg bowing—due to joint laxity early in life, fibular overgrowth later
- Spinal stenosis—due to reduced interpeduncular distance
- Obesity
- Cervical medullary compression—due to narrowing of foramen magnum
  - Maximum narrowing at 12 months of age, so all patients should get CT or MRI at that time

Discussion: radiographic findings

- Head
  - Relatively large calvarium
  - Frontal bossing and depressed nasal bridge
  - Narrowed foramen magnum
  - Cervicomedullary kinking

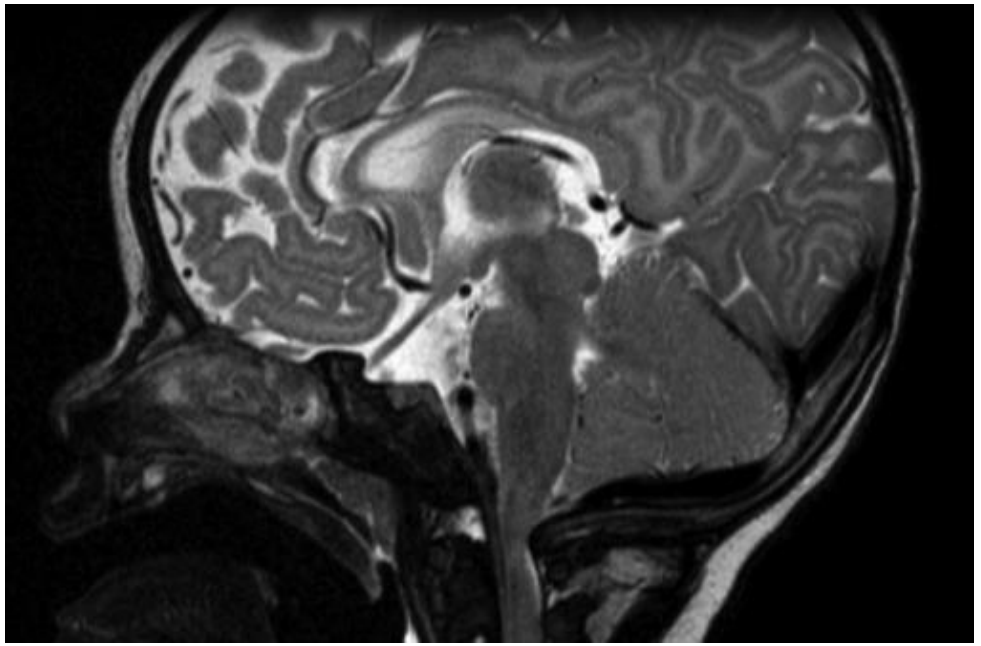


Image from https://radiopaedia.org/cases/achondroplasia-3

- Limbs
  - Rhizomelic shortening
  - Metaphyseal flaring
  - Long fibular relative to tibia
  - Trident hand
  - Chevron sign

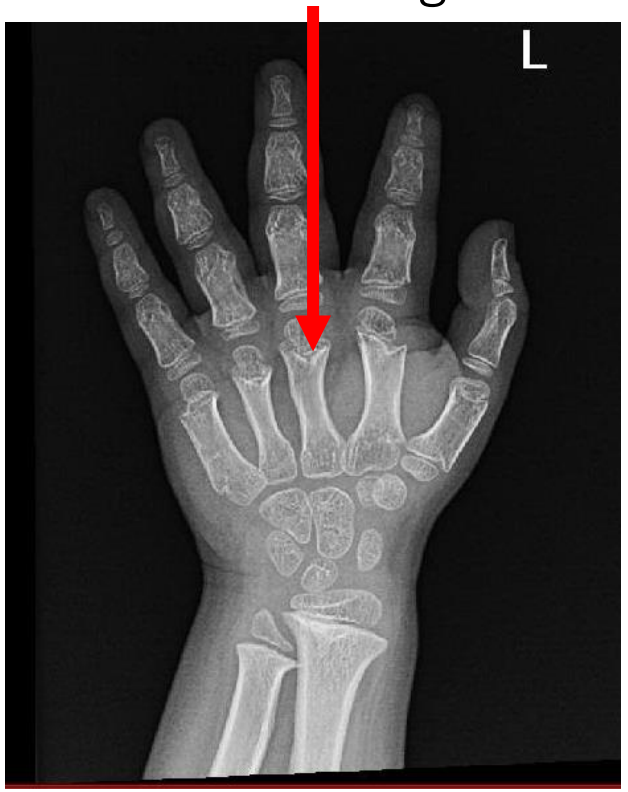


Image from Alenazi, Badi & Altamimim, Fatima & Albahkali, Mohammed. (2017). Growth hormone deficiency in a achondroplasia Saudi girl. Rare case report

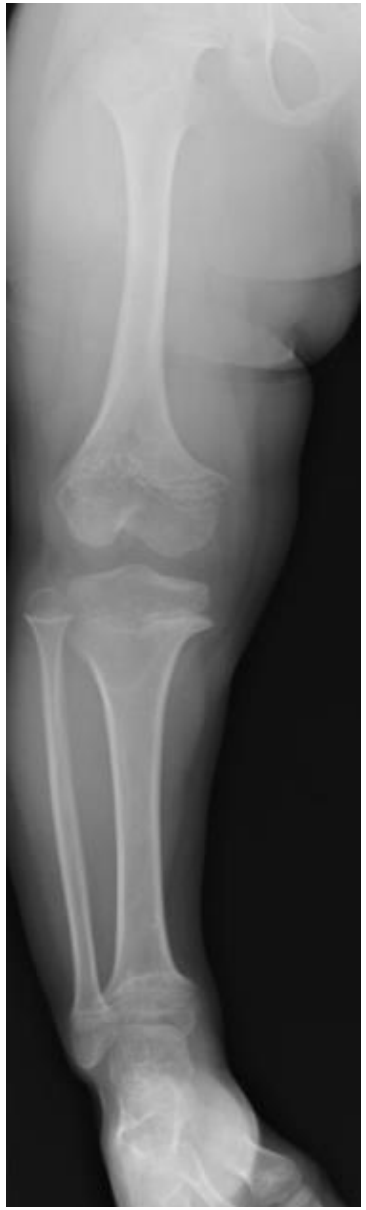


Image from https://radiopaedia.org/cases/achondroplasia-34

Discussion: radiographic findings

- Spine
  - Posterior vertebral scalloping
  - Short vertebral pedicles
  - Progressive caudal narrowing of interpedicular distance
- Chest
  - Narrow chest
  - Anterior flaring of ribs
- Pelvis
  - Squared “tombstone” or “mickey mouse ear” iliac wings
  - Small sacrosciatic notches
  - Flattened acetabular roofs
  - Narrow “champagne glass” pelvic inlet

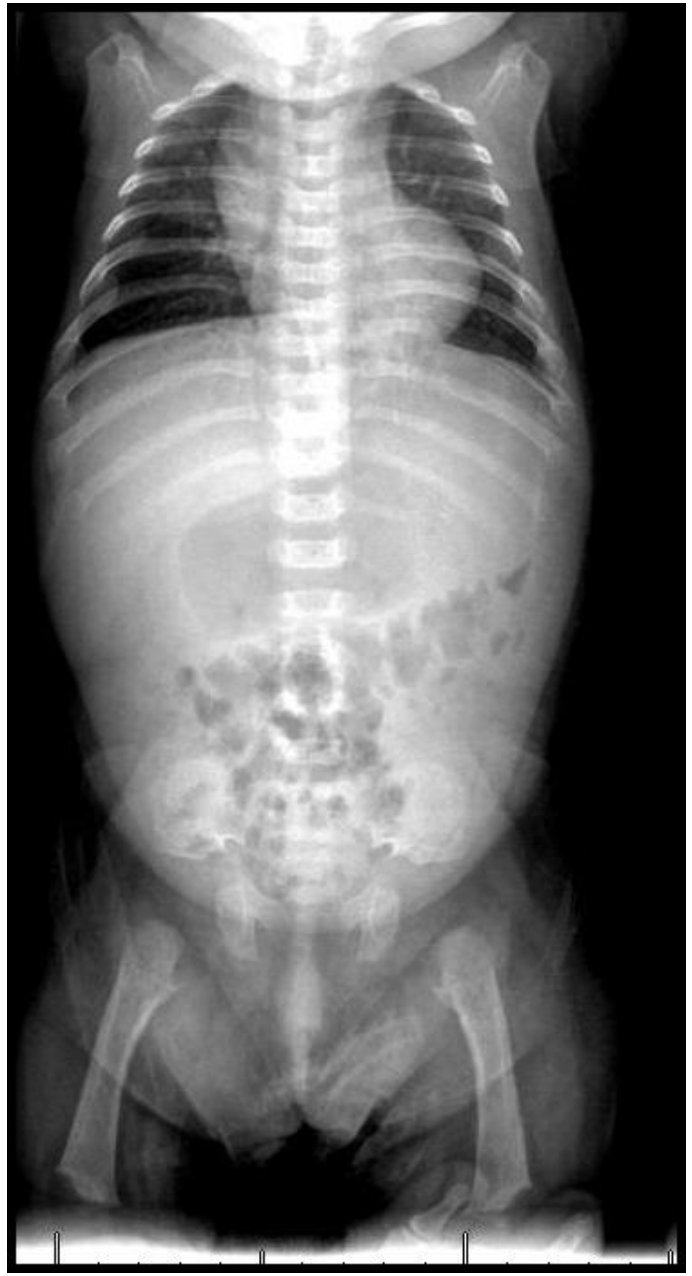


Image from https://www.uptodate.com/contents/image?imageKey=ALLRG%2F108749&topicKey=ALLRG%2F103825&search=achondroplasia&rank=1~150&source=see_link

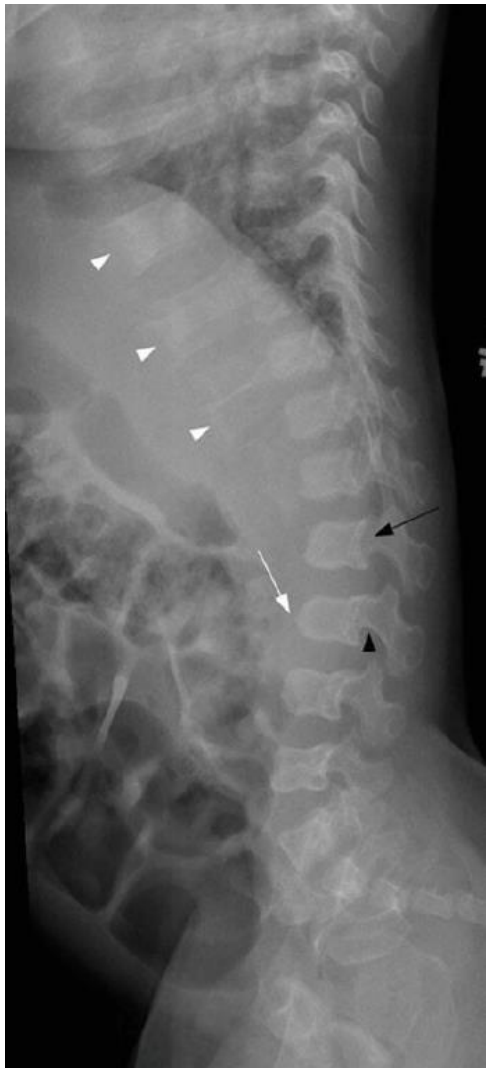


Image from Iyer RS, Chapman T. *Pediatric Imaging:The Essentials : The Essentials*. Wolters Kluwer Health; 2016.

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Discussion: management

- Physical therapy for motor developmental delay and leg bowing
- Occupational therapy, adjusted furniture, hand extenders, etc. for activities of daily living
- Limb lengthening—controversial
- Growth hormone—not recommended
- Experimental medication under investigation
- Low threshold for sleep studies, referral to ENT for tonsillectomy and adenoidectomy
- Neurosurgery—cervical medullary compression and spinal stenosis
- Aggressive management of otitis media
- Caesarean section for pregnancy

Bonus: severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)

Medical Terms	Other Names	Learn More: HPO ID
80%-99% of people have these symptoms		
Acanthosis nigricans	Darkened and thickened skin	0000956
Aplasia/Hypoplasia of the mandible		0009118
Brain atrophy	Brain degeneration [more]	0012444
Enlarged cerebellum		0012081
Generalized-onset seizure		0002197
Hypoplasia of the corpus callosum	Underdevelopment of part of brain called corpus callosum	0002079
Intellectual disability, severe	Early and severe mental retardation [more]	0010864
Metaphyseal chondrodysplasia		0005871
Severe global developmental delay		0011344

Figure from https://rarediseases.info.nih.gov/diseases/9443/severe-achondroplasia-with-developmental-delay-and-acanthosis-nigricans

- Caused by Lys650Met mutation in FGFR3[5]
  - Our patient was found to have a different mutation, so this is unlikely in our case

Wrap up

- Achondroplasia is the most common cause of dwarfism
- Caused by FGFR3 mutation
- Some clinical findings are short stature, distinctive facial abnormalities, and spinal abnormalities
- Several characteristic radiographic findings
- Delayed motor development, but normalizes by age 2-3
- Normal intelligence, life expectancy, and fertility
  - Given that no complications occur

References

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