İskelet Displazileri

Dr Rıza Madazlı

Cerrahpaşa Tıp Fakültesi Kadın Hastalıkları ve Doğum ABD Perinatoloji Bilim Dalı

- **Kemik ve kıkırdak / yapısal ve büyüme bozuklukları**
  - **Uzunluk**
  - **Şekil**
  - **Kıvam**

- **Kemik ve kıkırdak**
  - **Yapısal protein – Kollagen**
  - **Osteoblast, Osteoklast / Büyüme, Morfogenetik Fak**

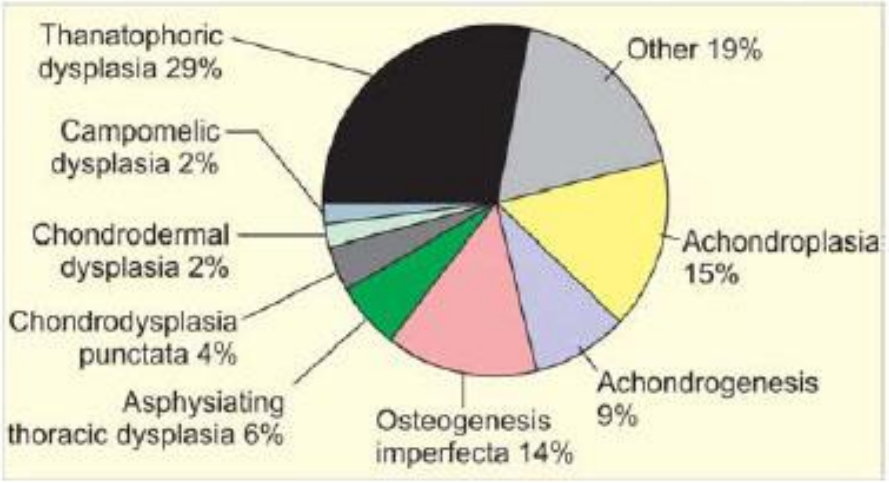
  ➔Gen Mutasyonları ➔ Isk Displazileri

- **Genetik**
- **Heterojen Grup**
- **>350 fazla tip – 160 gen belirlenmiş**

- İskelet Displazisi
  - 1 / 4000-5000 doğum
  - 21 / 30 000 (CTF)

  - Ö.Disp - 1 /10 000
    - %25 ölü doğum
    - %30 Erken Neonatal Ölüm
    - PNM 9.1/1000

- %70
  - Tanatotrofik displasi
  - Akondroplasia
  - Osteogenesis Imperfekta
  - Akondrogenesis



Genetik

- Otozomal dominant, resesif
- X-linked dominant, resesif

Hastalık	Gen Defekt
Achondroplasia, Thanatophoric dysplasia, Hypochondroplasia	Fibroblast growh faktör resöptör 3 (FGRR3)
Osteogenesis imperfecta	Prokollajen I (*COL1A1, COL1A2)*
Camptomelic dysplasia	SRY-box 9 protein (*SOX9*)
Achondrogenesis tip II, Hypochondrogenesis Kniest dysplasia	Prokollejen II (COL2A1)
Stickler dysplasia, Otospondylomegaepiphyseal dysplasia	Prokollejen XI (COL11A1 ve A2)
Acromesomelic	Cartilage morpogenic protein

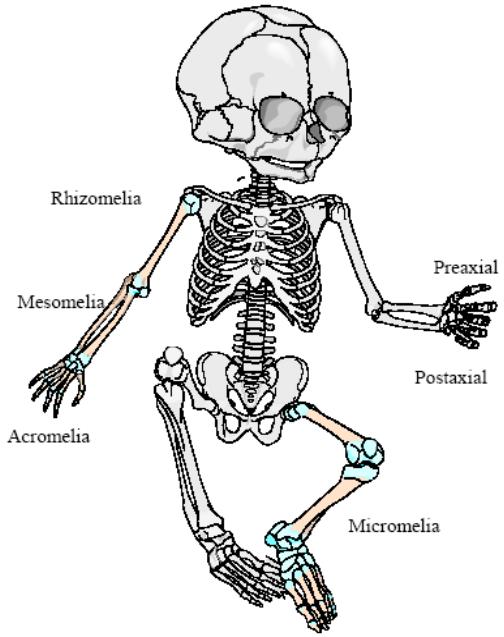
Hastalık	Gen Defekt
Hypophosphatasia	Alkaline phosphatase (*ALPL*)
Osteopetrosis	Carbonic anhydrase II (*CA2*)
Rhizomelic chondrodysplasia punctata, Zellweger syndrom	Peroxisomal biogenesis factors (PEX)
Diastrophic dysplasi Achondrogenesis IB Atelosteogenesis II	Diastrophic dysplasia sulfat trasporte (DTDST)
Depo hastalıklar	Spesifik gen mutasyon

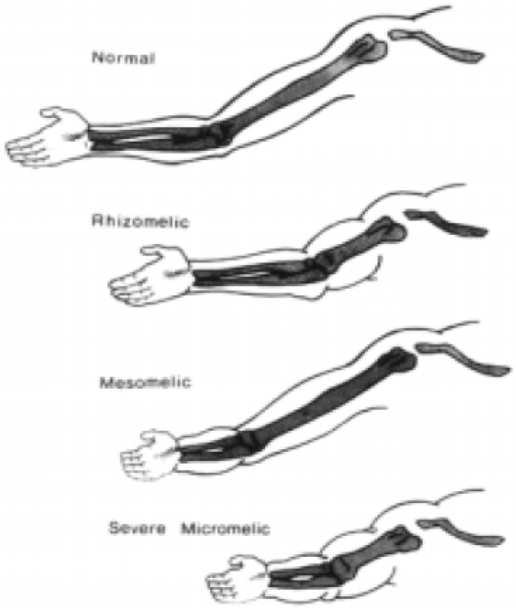
Tanımlar

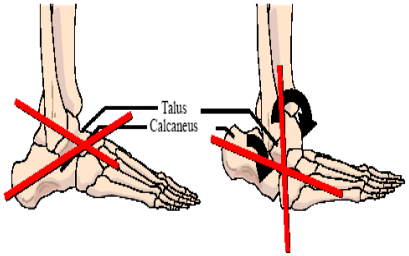
- **Rizomeli / Proksimal**
- **Mesomeli / Orta**
- **Akromeli / Distal**
- **Mikromeli / Ekstremite**

- **Polidaktili**
- **Sindaktili**
- **Clinodaktili**

- **Talipes**
- **Rocker - Bottom foot**







- **Diastrophic / Dönmüş**
- **Campomelic / Eğilmiş**
- **Metatropic / Değişen**
- **Kyphomelic / Öne eğilmiş**
- **Thanotropic / Ölüm getiren**
- **Spondylo- / Spine**

Prenatal Tanı

- **Prenatal Tanı**
  - **Zor / “Puzzle”**
  - **Tecrübe**
  - **Ekip**

  Prof Dr Beyhan Tüysüz (Çocuk genetik)

  Prof Dr Figen Aksoy (Patoloji)

- **%50-60 Antenatal belirti verir**

- **USG**
  - **Belirleme %94-96**
  - **Kesin Tanı (Adının belirlenmesi) - %30-50**

- **Aile Hikayesi**
  - **Ailede var**
  - **Kendi doğurmuş**

  ➔ Indeks vaka adı konmuş olmalı / Neyi aradığımızı biliyoruz

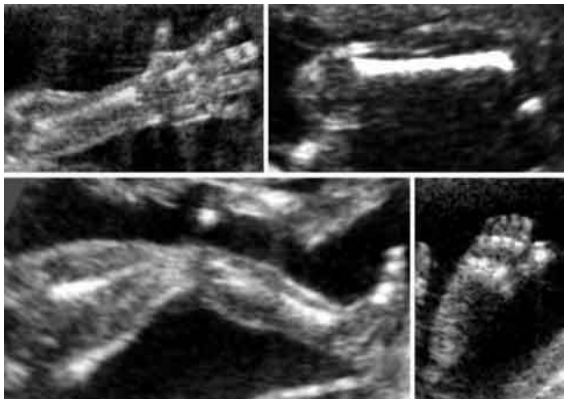
- **Mevcut gebelikte İskelet sorunu**

Yaklaşım

1. Uzun kemiklerin değerlendirilmesi
2. Eller ve ayaklar
3. Baş ve yüz
4. Göğüs kafesi
5. Omurga
6. Diğer kemikler
7. Polihidramnios, NIHF
8. Diğer sistem anomalileri

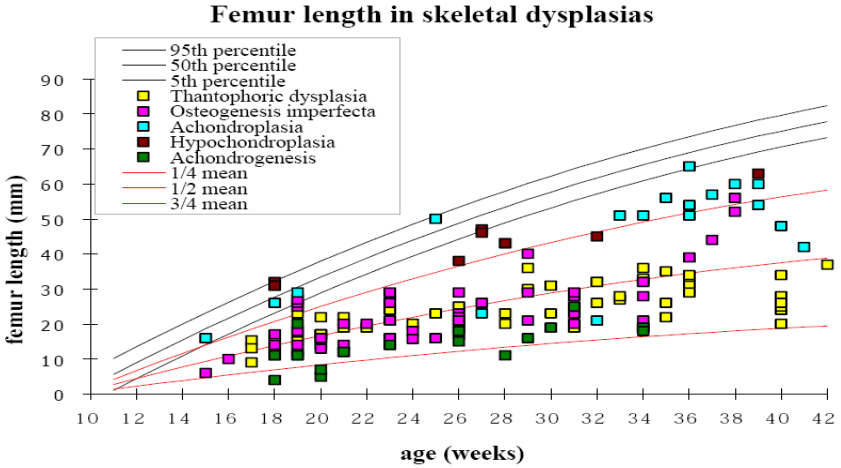
1. Ekstremiteler – Uzun Kemikler

- Uzun kemikler bakılmalı
  - 3 kemik / Üst ekstremite
  - 3 kemik / Alt ekstremite



- **Femur Ölçümü**

- FL<2sd
  - Yapısal
  - Kromozom
  - FGK
  - Izole
  - Iskelet Displasi / 2sd-5mm

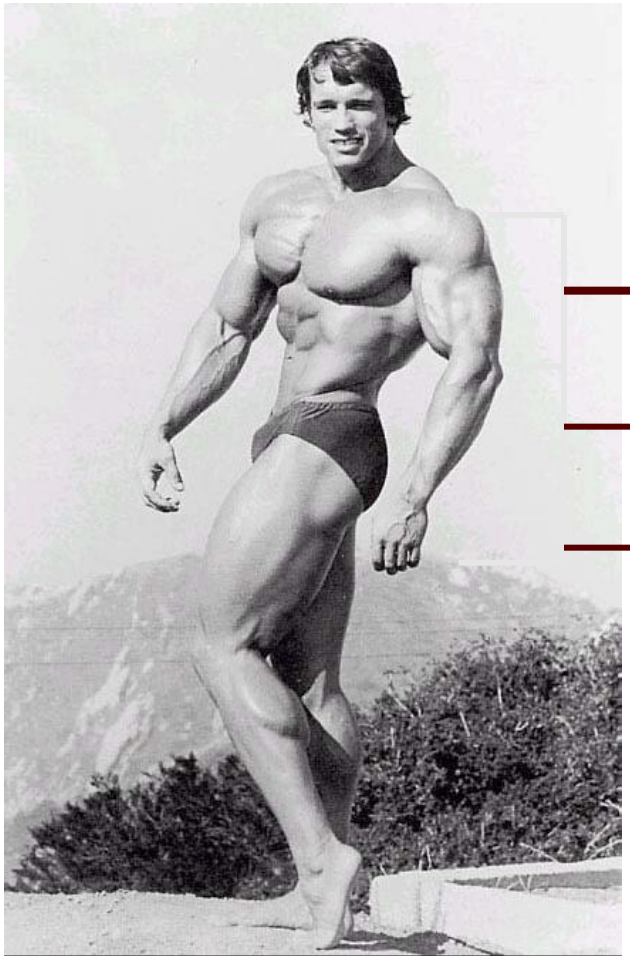


- Gelişim Hızı
  - 16-22 gh / 2.5-2.7mm /hf
  - OI / 15-16gh
  - Het. Achondroplasia- 27 gh

- Oranlar
  - FL /HC < -3sd
  - FL/Foot < 0.87

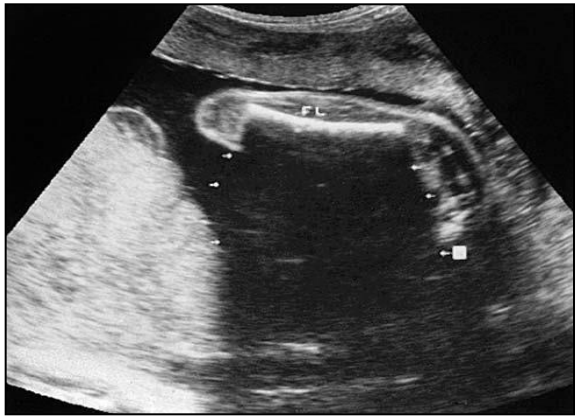
• Diğer Uzun Kemik Ölçümleri

Kısalık Tip	Ayırıcı Tanı
Rizomeli	Achodroplasia Chondrodysplasia punctata Diastrophic dysplasia Thanatophoric dysplasia Kısa femur
Mesomelia	Ellis-van Creveld syndrome Mesomelic dysplasia
Mikromelia	Achondrogenesis Atelosteogenesis Diastrophic dysplasia Fibrochondrogenesis Kniest dysplasia SRPD (I, III) Osteogensis imperfecta (II)



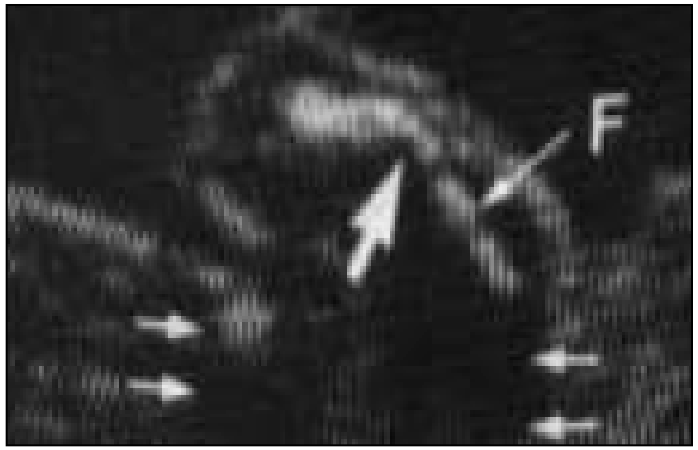
• Minerilizasyon (Ekojenite)

- **Akustik gölgelenme**
  - **Kalvaryum**
  - **Kaburga**
  - **Uzun kemikler**



- **Hipominerilizasyon**
  - **Achondrogenesis**
  - **Hypophosphatasia**
  - **Osteogenesis imperfecta**
- **Hipermінerilizasyon**
  - **Osteopetrosis**

- **Kırıklar**



Osteogenesis İmperfecta

- **Eğim (Bowing)**

- **Thanatophoric dysplasia**
- **Campomelic dysplasia**
- **Achondrogenesis**
- **Hypophosphatasia**

2. Eller /Ayaklar

- **Polidaktili**
  - **Asphyxiating thoracic dystrophy (Jeune syndrome)**
  - **Short-rib-polydactyly syndrome**
  - **Chondroectodermal dysplasia**
- **Sindaktili**
  - **Apert's syndrome**
  - **Jarcho-Levin syndrome**
  - **Robert's syndrome**
- **Talipes**
  - **Camptomelic dysplasia**
  - **Diastrophic dysplasia**
  - **Osteogenesis imperfecta**

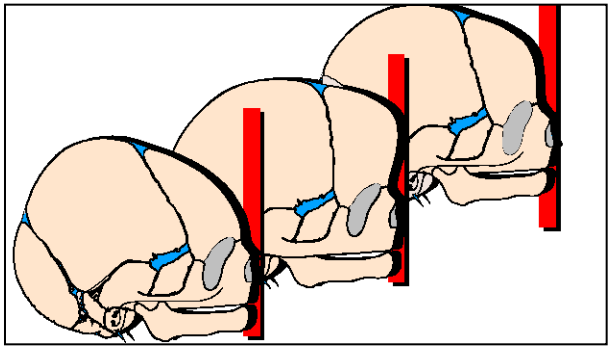
3. Kafa

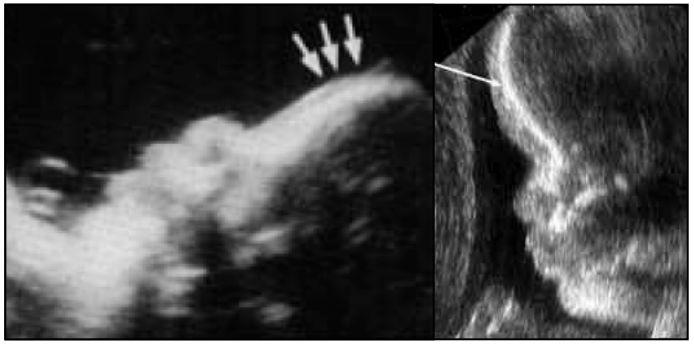
- **Baş Şekli**

- **Frontal bossing**
  - **Thanatophoric dysplasia**
  - **Osteogenesis imperfecta**

- **Cloverleaf skull**
  - **Homozygous achondroplasia**
  - **Thanatophoric dysplasia**

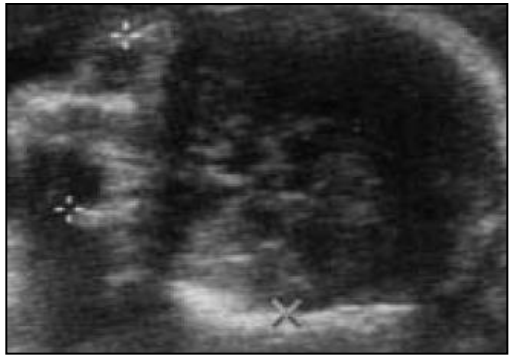
- **Craniosynostosis**
  - **Carpenter's syndrome**
  - **Hypophosphatasia**
  - **Acrocephalosyndactyly**
  - **Crouzon – Aperts**

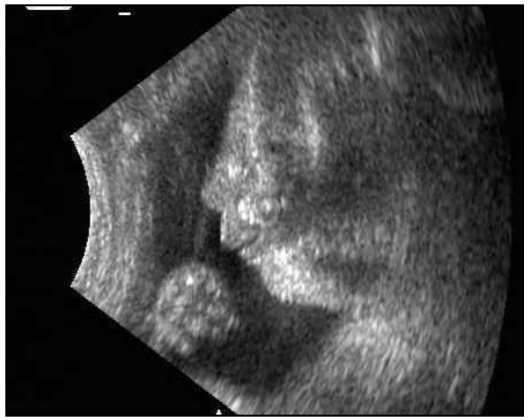




- **Yüz**

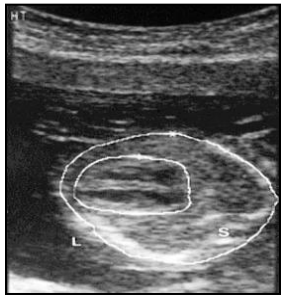
- **Göz**
  - **Hipo ve hipertelorizim (Üçler Kuralı)**
- **Mikro-retrognati**
- **Yarık dudak, damak**
- **Kulaklar**

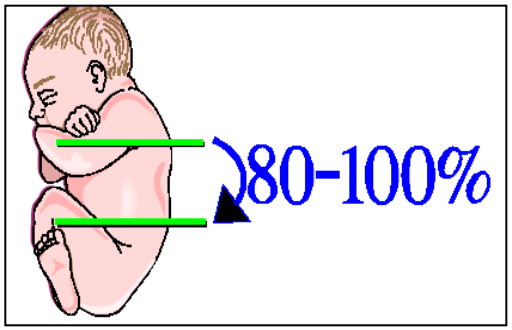




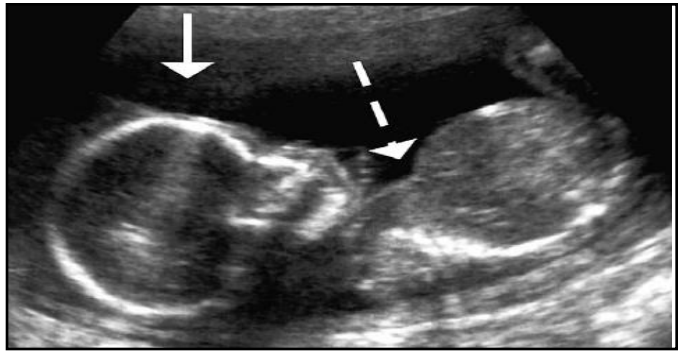
4. Göğüs

- GÇ / AÇ ➔ % 80-100
- Lethal İskelet Displazi / % 50



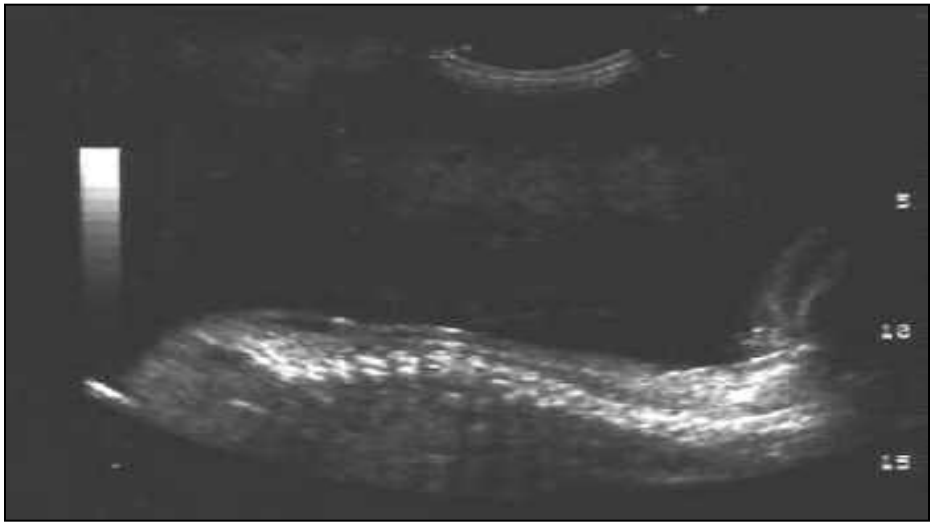


- Dar thoraks
  - Achondrogenesis
  - Hypophosphatasia
  - Campomelic dysplasia
  - Chondroectodermal dysplasia
  - Osteogenesis imperfecta
  - Short-rib polidaktili
  - Asphyxiating thoracic dysplasia



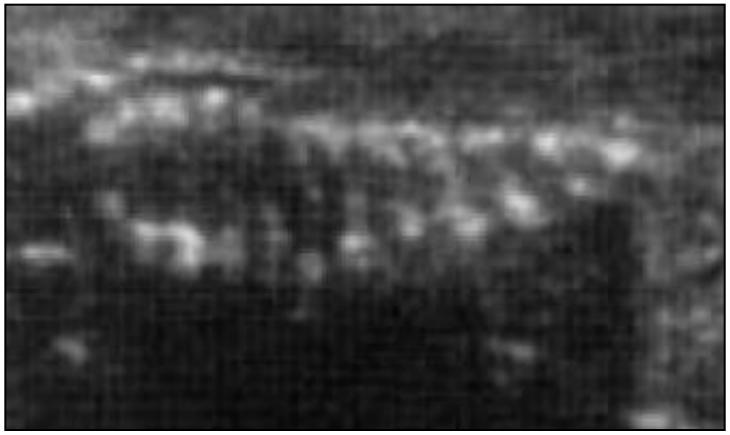
5. Omurga

- **Platyspondyly – Omurganın düzleşmesi**
  - **Thanatophoric dysplasia**
  - **Achondroplasia**
- **Hipominerelizasyon-**
  - **Achondrogenesis**
- **Hemivertebra –**
- **Kyphosis**
- **Scoliosis**



6. Diğer Kemikler

- Scapula
  - Hipoplazik/ Campomelic dysplasia
- Klavikula
  - Kısa / Cleidocranial dysplasia
- Kaburga
  - Kısa / SRPS
  - Sayı / 11 çift- Camptomelic dysplasia, Cleidocranial dysplasia, Trisomy 18
- İliac kemikler



7. Diğer Anomaliler

- Polihidramnios
  - Thanatophoric dysplasia
  - Achondroplasia
  - Chondrodysplasia punctata
  - Short-rib-polydactyly syndrome
  - Achondrogenesis
- NIHF
- Diğer Sistemler – Kalp, Böbrek
- Fetal Hareketler

- **Göğüs Çevresi / Abdomen Çevresi oranı ≤ 0. 6**

- **Femur Uzunluğu / Abdomen Çevresi oranı ≤ 0.16**

Perinatal Ölümcül Displasi

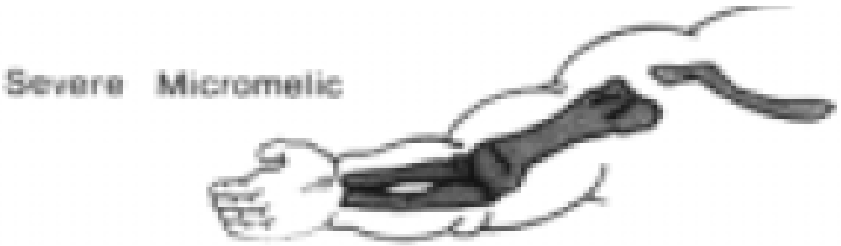
Diagnosis	Long bones	Thorax	Hands and feet	Skull	Spine	Short Trunk	Fracture	Bone Mineralisation	Gene mutations	Other
Thanatophoric dysplasia	Length 30-80% of the mean for GA; telephone-receiver femora	Hypoplastic; short ribs	Short	Frontal bossing, clover leaf skull	Platyspondyly	No	No	Decreased spine ossification	FGFR3* (AD)	Hydrocephaly; polyhydramnios
Achondrogenesis	Length < 30% of the mean for GA*	Narrow thorax; rib fractures	Short	Macrocrania	Squared iliac wings	Yes	Occasional	Partial or complete lack of ossification of calvarium, spine and ischial bones	COL2A1* Type1: AR* Type2: AD*	Hydrops; polyhdramnios
Osteogenesis imperfecta	Normal limb length,		Short	BPD£5th centile for GA*; thin skull; deformation after compression	Not specified	Yes	Few to 100	Decreased bone mineralization in late 3rd trimester	COL1A1*, COL1A2* (AD)*	Blue sclerae
type I (mild)		Short; rib beading (wavy ribs)								2A: dark blue 2B: light blue
type II (lethal)	Length 30-80% of the mean for GA*						Multiple	Markedly decreased bone mineralization		Blue at birth, becoming normal with age
type III (severe)	Progressive shortening: length 80-100% of the mean for GA*						Multiple	Decreased bone mineralization		
Chondrodysplasia Punctata	Rhizomelic shortening of the otherwise straight long bones, multiple epiphyseal stippling	Normal	Not specified	Flat face, micrognathia, microcephaly	Not specified	Not specified	Not specified	Normal	(AR)*	Severe mental retardation

Diagnosis	Long bones	Thorax	Hands and feet	Skull	Spine	Short Trunk	Fracture	Bone Mineralisation	Gene mutations	Other
Diastrophic Dysplasia	Micromelic dwarfism, metaphyseal widening of the shortened tubular bones	Normal	Clubfeet, hitchhiker's thumb	Micrognathia, cleft palate	Kypho-scoliosis,	Not specified	Not specified	Decreased	DTDST* SLC26A2* (AR)*	Not specified
Short-rib polydactyly syndromes	Severe micromelia	Small, short ribs	Polydactyly	Normal	Not specified	Not specified	Not specified	Normal	(AR)*	Cardiac and genitourinary abnormalities
Camptomelic dysplasia	Ventrally bowed short femur and tibia	Small	Clubfeet	Micrognathia, cleft palate	Not specified	Hypo-plastic scapula	Not specified	Normal	SOX9*, (AD)*	Laryngotracheomalacia, cardiac, brain,renal abnormalities
Fibrochondrogenesis	Micromelia with metaphyseal flaring (dumbbell shape)	Small	Short	Normal size, demineralized, flat face	Platyspondyly, midline clefts	Not specified	Not specified	Decreased bone mineralization	(AR)*	Not specified
Atelosteogenesis	Severe micromelia, bowed long bones	Narrow, short ribs	Short	Flat face,facial clefts	Not specified	Not specified	Not specified	Decreased bone mineralization	Not specified	Not specified
Hypophosphatasia congenita	Severe micromelia	Narrow, short ribs	Short	Normal size, demineralized, compressible	Not specified	No	Occasional	Patchy or generalised demineralisation	TNSALP*, (AR)*	Not specified

Postnatal

- **Ekip**
  - **Perinatolog**
  - **Genetisyen**
  - **Patalog**
- **Fizik muayene**
- **Radyografi**
- **Histolji / Otopsi**
- **Kromozom / Spesifik sitogenetik çaılşmalar**
- **DNA**
- **Biyokimyasal - Enzimatik çalışmalar**

• MİKROMELİ

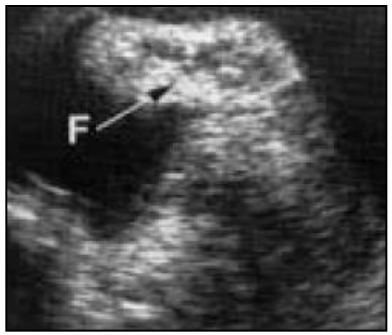


Achondrogenesis

- **Tip I**
  - **Ağır mikromegali**
  - **Dar, kısa thoraks**
  - **Kaburga kırıklar**
  - **Kafa ve vertebral kemiklerde hipominerilizasyon**

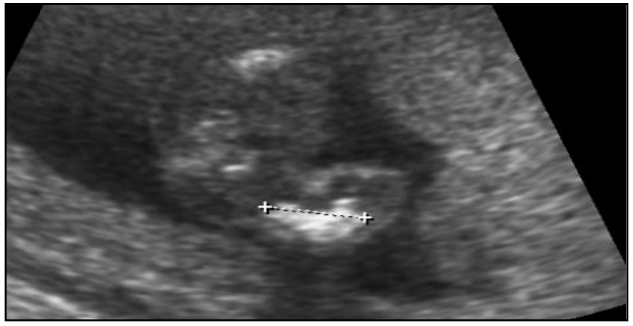
- **Tip II**
  - **Uzun kemikler kısalık değişken**
  - **Kafa ve vertebral osifikasyon nisbeten normal**
  - **Kaburga kırık yok**

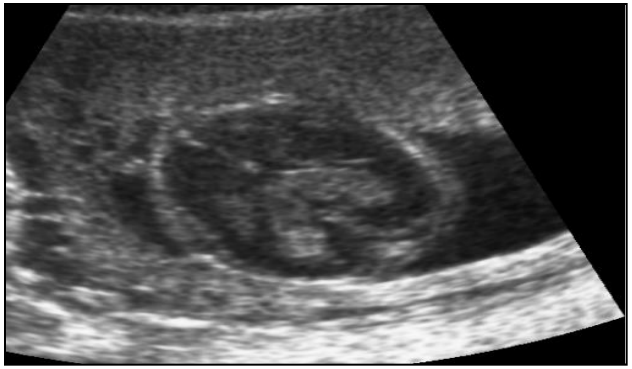
  - **Polihidramnios**
  - **NIHF**



Osteogenesis Imperfecta

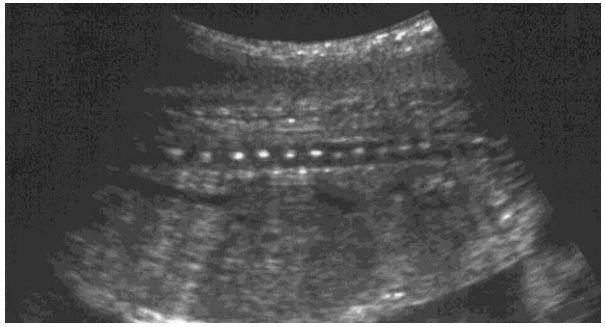
- **Micromelia**
- **Hipominerilizasyon**
- **Kırıklar nedeniyle deforme uzun kemikler**
- **Kaburga kemikleri kısa ve kırıklar**
- **Dar thoraks**





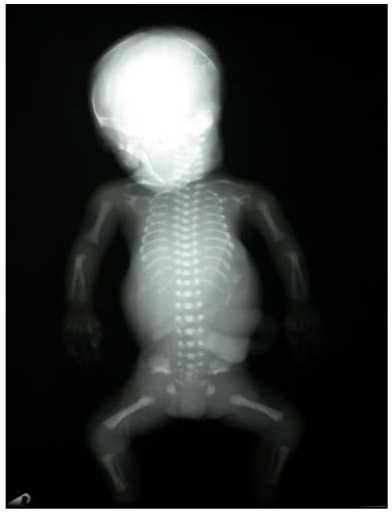
Hpophosphatasia

- **Kafa hipominerilizasyon**
- **Uzun kemikler kısa, kırıklar, angülasyon**
- **Dar thoraks**
- **Polihidramnios**



Short Rib Polidaktili sendromu

- **Ağır mikromelia**
- **Dar kısa thoraks**
- **Kısa kaburga kemik**
- **Polidaktili**
- **Polihidramnios**

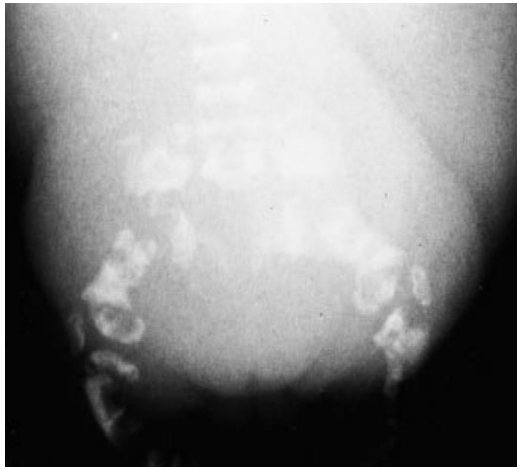


Atelosteogenesis

- **Ağır mikromelia**
- **Dar thoraks**
- **Omurga anomalileri**
- **Kısa parmaklar**

Greenberg Dysplasia

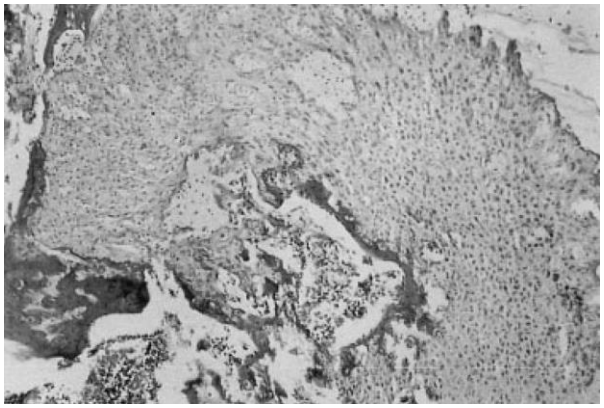
- **Mikromelia**
- **Dar thoraks**
- **Güveyeniği görünümü**

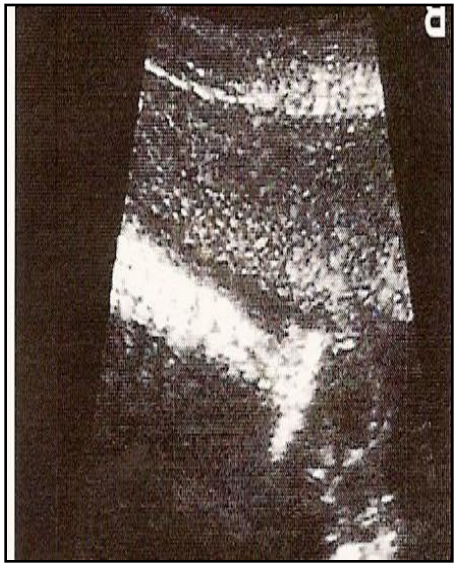


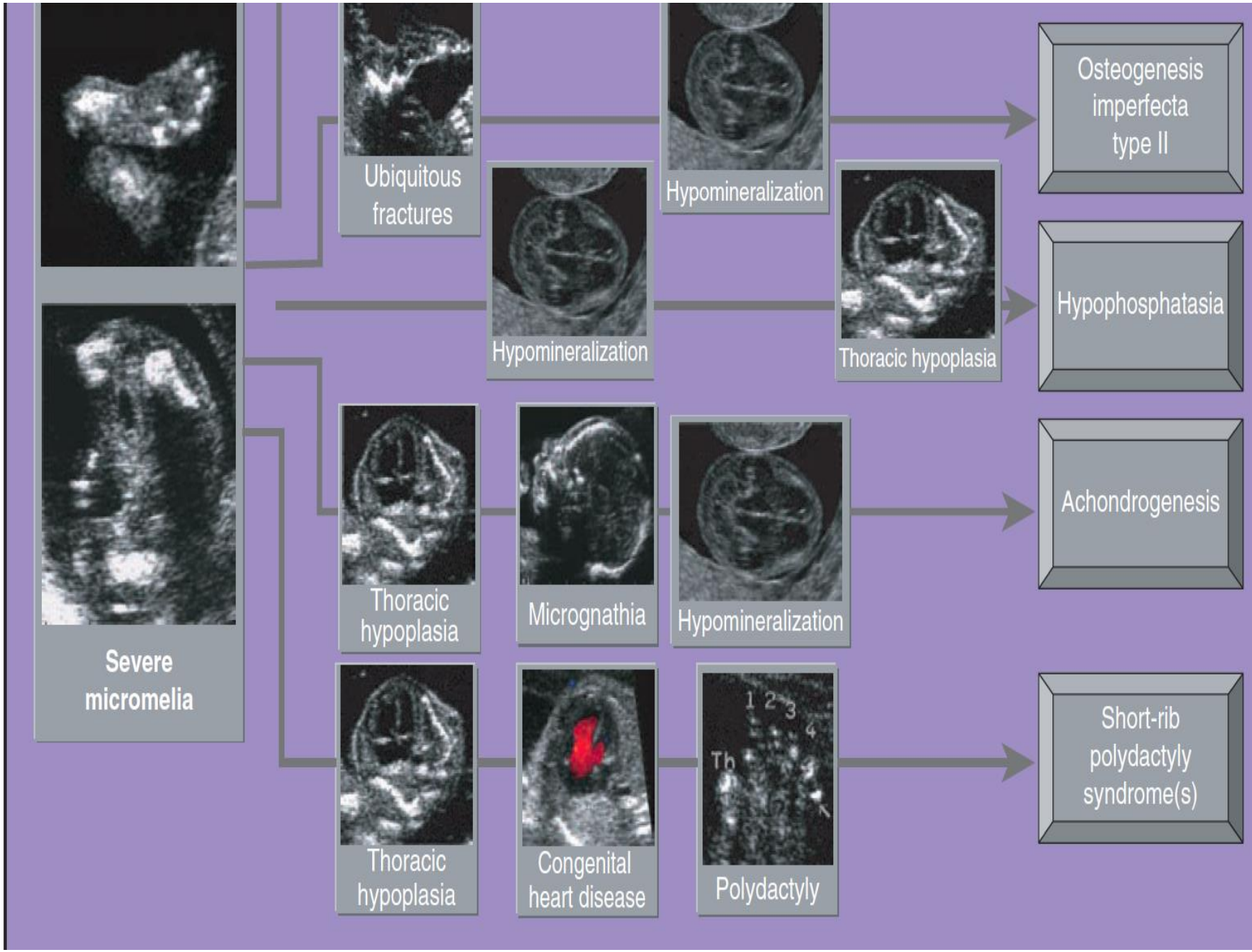
Detailed ultrasonographic findings in Greenberg dysplasia

Riza Madazli*, Figen Aksoy, Vildan Ocak and Turgay Atasü

Prenat Diagn 2001; **21**: 65–67.



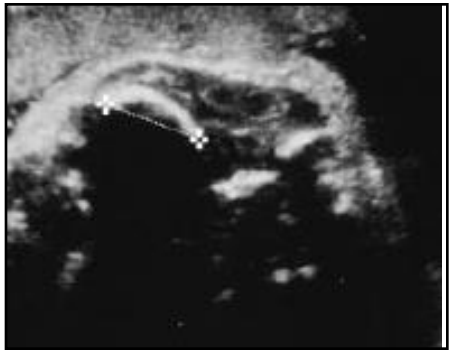


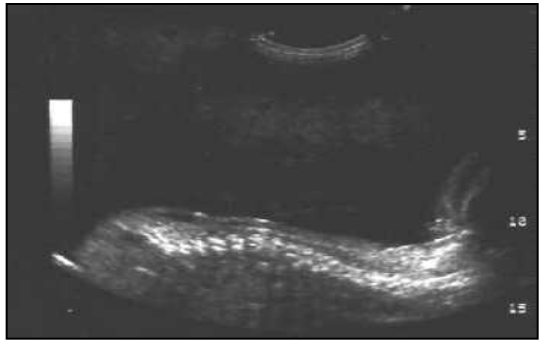

Severe micromelia
Ubiquitous fractures
Hypomineralization
Osteogenesis imperfecta type II
Hypomineralization
Thoracic hypoplasia
Hypophosphatasia
Thoracic hypoplasia
Micrognathia
Hypomineralization
Achondrogenesis
Thoracic hypoplasia
Congenital heart disease
Polydactyly
Short-rib polydactyly syndrome(s)

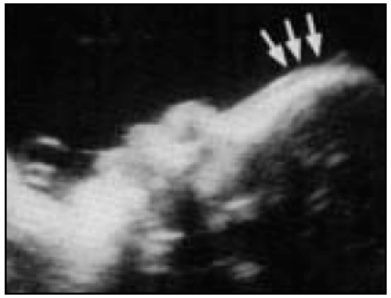
• RİZOMELİ

Thanatophoric Displasia

- **Ağır rhizomelia**
- **Uzun kemik eğik (bowed) “ telephone receiver”**
- **Thoraks dar, normal uzunluk**
- **Frontal bossing**
- **Cloverleaf skull**
- **Platyspondyly**
- **Polihidramnios**

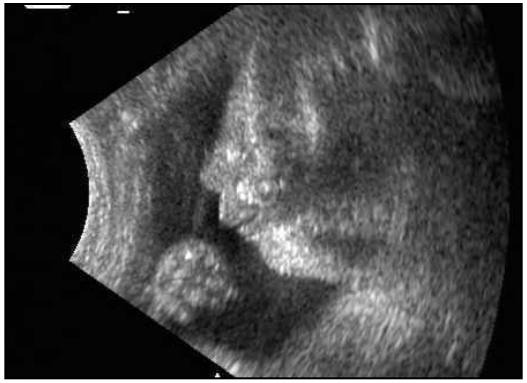


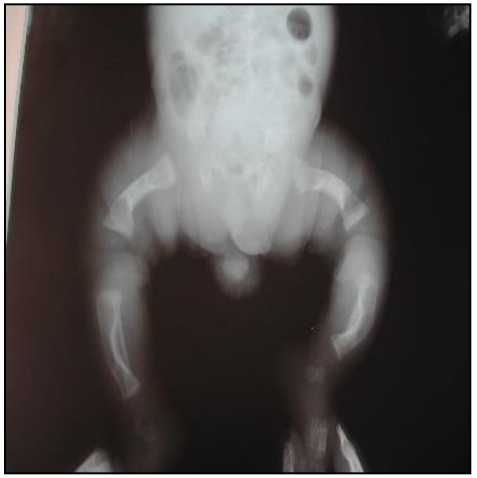




Campomelic Displasia

- **Eğimli (bowed) uzun kemikler**
- **Scapula hipoplazik**
- **Polihidramnios**
- **Mikrognati**





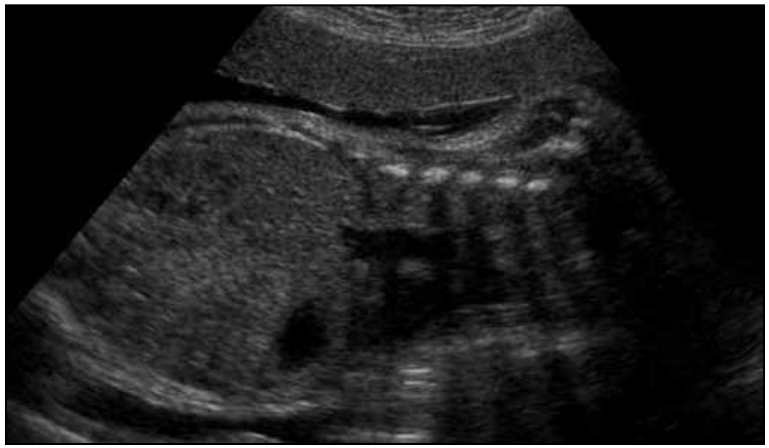
Achondroplasia

- Heterozygous Achondroplasia
  - Frontal bossing
  - Burun kökü basık
  - Goğüs normal
  - Rhizomelia (>24 gh / alt ekst. önce)
  - Parmaklar eşit uzunluk

- Homozygous Achondroplasia
  - Rhizomelia, ağır
  - Thoraks dar
  - Frontal bossing
  - Burun kökü basık

Asphyxiating Thoracic Dystrophy (Jeune)

- **Uzun kemikler kısa (orta derecede)**
- **Dar, uzun thoraks**
- **Polidaktili, yarık dudak**
- **Üriner anomali**



Clinical Variability of Asphyxiating Thoracic Dystrophy (Jeune) Syndrome: Evaluation and Classification of 13 Patients

Beyhan Tüysüz,[1]* Safa Barış,[1] Figen Aksoy,[2] Rıza Madazlı,[3] Savaş Üngür,[4] and Lale Sever[5]

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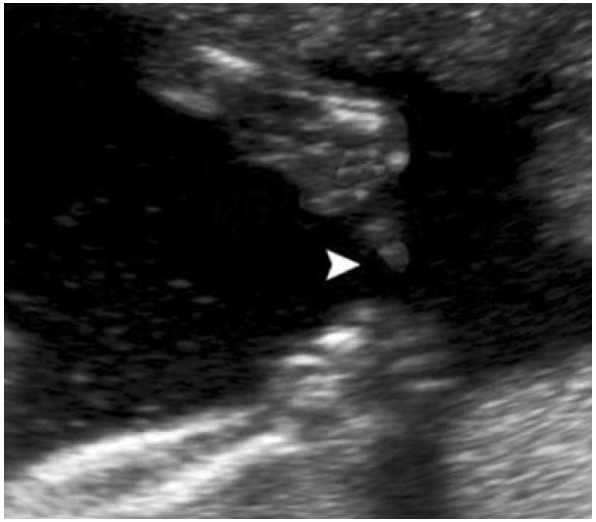
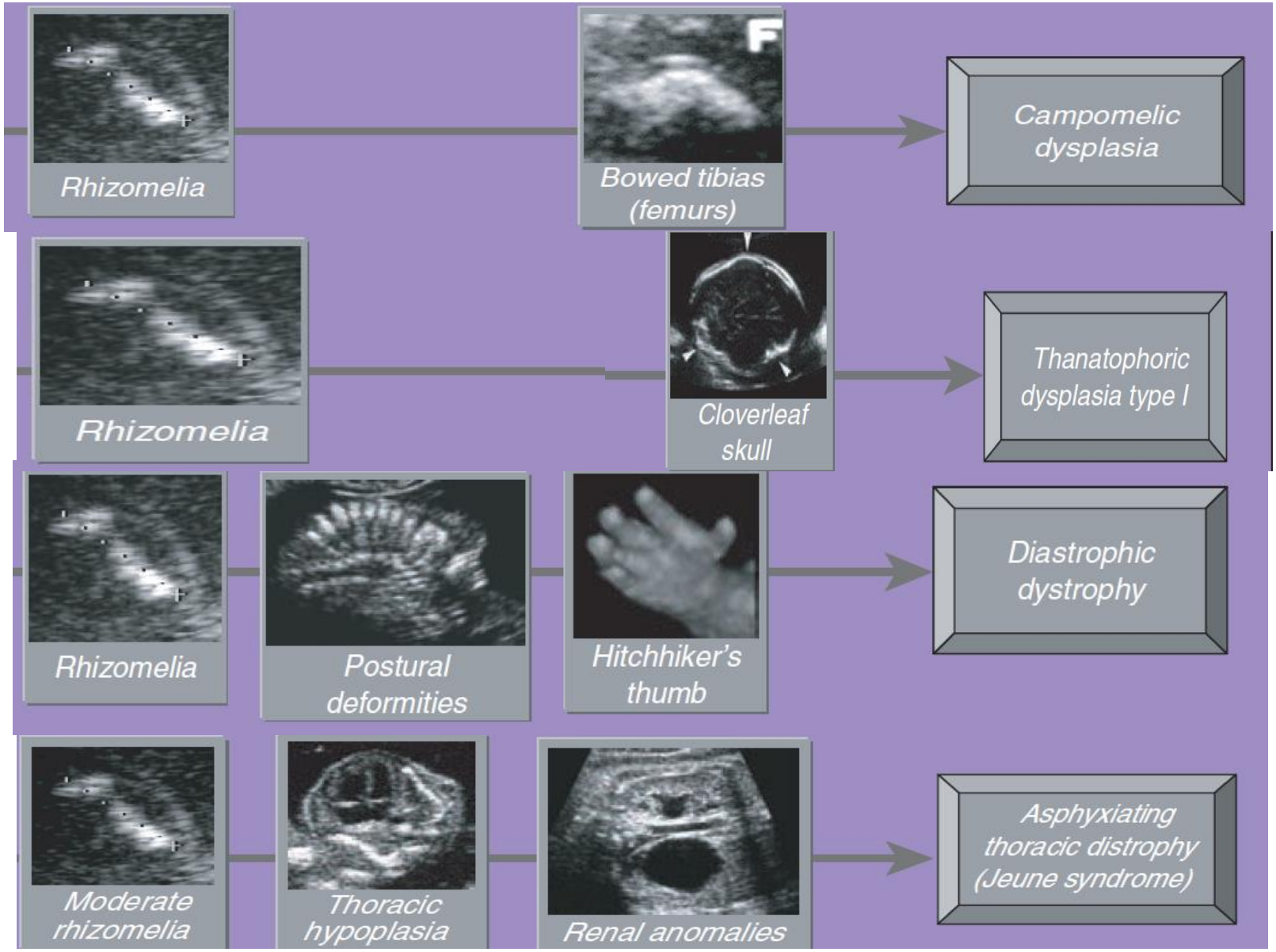
FIG. 2. Patient 8 at the age of 12 years. Note the severe narrow long thorax (a,b), and the severe shortness of hands (c,d). [Color figure

Diastrophic Dysplasia

- **Uzun kemikler kısa / Rizomelik (Orta derecede)**
- **El- ayak deformiteleri**
- **Eklem deformiteleri**
- **Skolyoz**




Rhizomelia
Bowed tibias (femurs)
Campomelic dysplasia
Rhizomelia
Cloverleaf skull
Thanatophoric dysplasia type I
Rhizomelia
Postural deformities
Hitchhiker's thumb
Diastrophic dystrophy
Moderate rhizomelia
Thoracic hypoplasia
Renal anomalies
Asphyxiating thoracic distrophy (Jeune syndrome)

Teşekkürler