

# Skeletal Dysplasia: Approach to Simplify Diagnosis, Looking for Radiographic Clue Signs

## Abstract:

Skeletal dysplasia is a heterogeneous group of disorders affecting the growth of bones and cartilage. Diagnosis can be difficult for many reasons; they are over 400 diseases, and some are rare and might have atypical presentation when clinical manifestations and radiological findings might not match the classical picture of the specific disorder. The final diagnosis of a skeletal dysplasia is a combined workup that includes clinical examination, family history, radiological assessment (skeletal survey and other investigations), and finally with the laboratory, molecular and genetic assessment. These all steps require tertiary centers, therefore, the primary clinical practice would require a tool-kit to help identify the most common skeletal dysplasia easily and identify the most important features of uncommon or rare disorders. The combined clinical assessment and radiological assessment can together reach this goal. The aim of this article is to spotlight on few important checkpoints to help the clinician and radiologist to narrow the differential diagnosis in the primary evaluation before the referral, if available, for molecular and genetic study. This article will focus on essential initial steps in diagnosis and some clue diagnostic features in the skeletal survey images that are classic for the most common disorders. This article will focus on essential initial steps in diagnosis and some clue diagnostic features in the skeletal survey images that are classic for the most common disorders.

**Key words** #skeletal, # dysplasia, #skeletal survey, #achondroplasia, # diagnosis, # radiology

## **Introduction**

Skeletal Dysplasia is a heterogeneous group of conditions mainly characterized by abnormal bone and/or cartilage development and growth. According to estimates, there are 1/5000 live births each year overall [1]. Since 1950, skeletal dysplasia disorders have undergone many classifications to categorize them according to the clinical presentation, radiological features, and the inheritance/genetic pathway. In 1970, the "International Nomenclature of Constitutional Diseases of Bone" group classified dysplasias as per the clinical and radiological features and gradually introduced the molecular. In 1997 the new Nomenclature introduced the genetic

categories as which gene and specific protein is affected in each group and disorder. [2] This Nomenclature underwent many regular updates with the latest in 2019 that maintained the 42 number of the groups of the disorders, however, increased to a total of 461 disorders classified under umbrella of skeletal dysplasia. Almost 437 genes showed mutations in 425 of the disorders in the latest 2019 list [3]. In daily practice at primary care centers, the clinician is the first line who receive the patient, check **clinical family history, examine thoroughly the patient and skeletal survey for systematic thorough radiologic assessment of patients with short stature or dysmorphic features. The general radiologist, in turn,** would tailor each skeletal survey as per the clinical suspicion. The initial categorization would help the clinicians to know if it is skeletal dysplasia or not and would help them plan their treatment and diagnosis workup. The approach depends on a few important checkpoints. Some of the dysplasias are lethal when patients would be stillborn or die shortly in neonatal period, while others are nonlethal. First question the clinician would ask is if it is truly a skeletal dysplasia or only a cluster of musculoskeletal features of a multisystem disease. Then the clinician will perform a crucial complete clinical assessment to look for any dysmorphic clinical features or disproportionate body parts. Later, the clinician would request a skeletal survey in which the radiologist will select several anteroposterior and lateral views to cover the entire skeleton and to help identify the main features of bone, limbs, or spine abnormality. Furthermore, few cardinal signs related to specific characterized shapes can be identified. An overall assessment of bone mineralization can help distinguish some dysplasias. **The approach is in two parts: clinician's and radiologist's role.**

### **I-Clinical Assessment:**

Onset: almost 100 out of the 400 disorders are present in fetal life and at birth [4], therefore, the prenatal assessment would help families and clinicians be prepared for the management of lethal and severe disorders with many organ dysfunctions expected. Measurements and ratios of limbs

and body parts in different positions would help to identify the disorder, especially when combined with detecting which parts of the limb are affected, rhizomelic, mesomelic, or acromelic. These important pieces of information would help to narrow the list of differential diagnosis. Lastly, to check other organs' involvement for instance, external, like the teeth, eyes, palate, and hair, and even check for abdominal organomegaly. [5].

**II- Radiologic Assessment:** The radiologist will tailor the skeletal survey as per the clinician's suspected diagnosis. The "genetic" skeletal survey usually should include all the following x- rays: skull: AP & lateral views, spine: AP & lateral views, pelvis: AP view, extremities: AP

view, hands, and feet: AP view [5,6]. It is recommended to add a lateral knee view to exclude multiple epiphyseal dysplasia [5,7]. Images will be assessed for bone density (maintained, decreased, or increased), what bones are involved if solely or combined (axial, appendicular, flat bones, or long bones), what part of the long bone is involved (metaphyseal, diaphyseal, or epiphyseal), the part of the limb involved (rhizomelic, mesomelic or acromelic), and to look for cardinal signs. We will go through some examples.

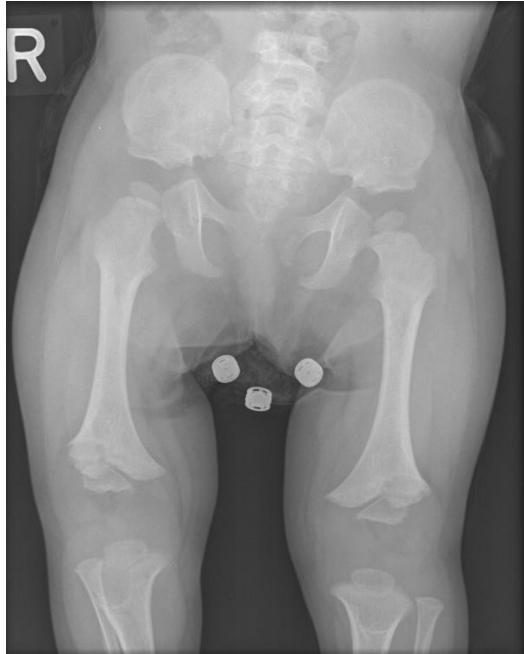
**Bone mineralization assessment** on plain x-ray is subjective and less reliable in digital radiography. However, it can add an important piece of information to the radiologist to better classify the skeletal dysplasia disorder. For instance, the most common non-lethal skeletal dysplasia; achondroplasia (FGFR3 chondrodysplasia group 1) has maintained bone density (Fig.1,a). (7,8). Unlike, OI (osteogenesis imperfect and decreased bone density group 25) in which bone demineralization is characteristic and can be detected on antenatal ultrasound. The improved visibility and details of intracranial structures reflects the demineralized low echogenic skull bones and help the diagnosis [A] (Fig.1,b). Decreased cortical bone thickness and accentuated bone trabeculae [B]. Similar signs of decreased bone density is noted in MPS (Lysosomal storage diseases with skeletal involvement group 27)

(Fig.1,c). The hallmark of osteopetrosis (osteopetrosis and related disorders group 23) is dense bones, which are brittle, multiple fractures and different age of callus formation is noted (Fig.1,d).

Fig. 1. Bone mineralization and long bones morphology.

a. Achondroplasia,

b. OI



c. MPS,

d. Osteopetrosis



**Location** in the long bone if metaphyseal, diaphyseal, or epiphyseal. In chondrodysplasia punctate (group 21), for instance, epiphyseal sole involvement, and the punctate morphology are classic, (Fig. 2). While in Pyle disease (other sclerosing bone disorders group 24), only metaphysis with or without diaphysis is involved [11]. (Fig. 3). When the spine is involved with long bones, it can be with metaphysis, named spondylometaphyseal dysplasia (TRPV4 group 8), or epiphysis, it is named: spondyloepiphyseal dysplasia congenita (SEDC) (type 2 collagen group 2).

Fig. 2 Chondrodysplasia punctate: epiphyseal involvement.

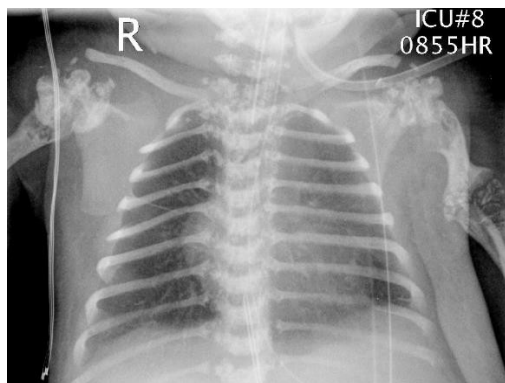


Fig. 3 Pyle disease, metaphyseal dysplasia

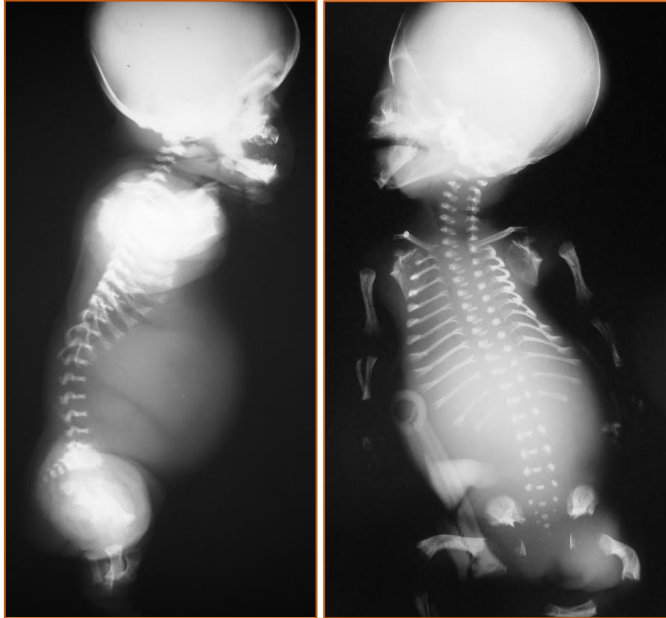


**Lethal dysplasia:** despite being rare, knowing the most characteristic features of lethal skeletal dysplasias is important to the diagnosis of babygram or stillborn image. The incidence of lethal skeletal dysplasias is around 0.95 per 10,000 deliveries [6]. The most common lethal dysplasias are thanatophoric dysplasia (chondrodysplasia group 1. FGFR3), (Fig. 4, a), and osteogenesis imperfecta, II (osteogenesis imperfecta and decreased bone density group 25), (Fig. 4, b). Others are hypophosphatasia (group 26, Abnormal mineralization group), achondroplasia

(chondrodysplasia group 1), short rib–polydactyly syndrome (SRPS) type 1 (Saldino–Noonan) (iliopathies with major skeletal involvement group 9) (Fig. 4, c).

Fig. 4 Lethal Dysplasias

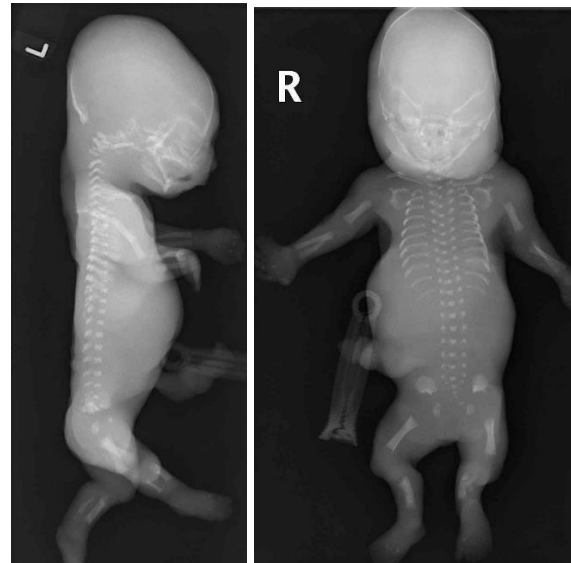
a. Thanatophoric Dysplasia: Macrocephaly, micromelia, small cone-shaped thorax, platyspondyly, short limbs, and typical telephone receiver shaped femur.



b. OI type II, death due to respiratory deficiency



c. Saldino Noonan: small, long narrow thorax result in asphyxiating thoracic dystrophy



### **Cardinal Features in Skeletal Survey:**

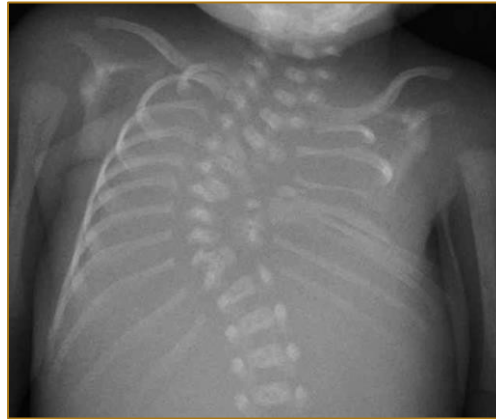
**Spine** anteroposterior and lateral views are part of the skeletal survey and assessed systematically. This includes localizing the abnormal vertebrae if focal or diffuse, vertebral body height to exclude platyspondyly (Fig. 5, a), integrity of ossification centers, and any pattern of abnormal segmentation (Fig. 5, b) [10]. Some specific features in mucopolysaccharidosis can direct the diagnosis confidently into a specific subtype; as the vertebral body beaking is central in Morquio syndrome (Mucopolysaccharidosis IV) (Fig. 5, c). [12]. while it is anteroinferior in Hurler's syndrome (Mucopolysaccharidosis I) [13]. (Fig. 5, d). The dorsolumbar vertebrae show coronal cleft in chondrodysplasia punctata [14]. with no platyspondyly. Platyspondyly is present, however, in spondyloepiphyseal dysplasia tarda (spondylo-epi-(meta)-physeal dysplasias group 13). (Fig. 5, e). In pyknodysostosis, the hyperdense vertebrae show prominent anterior defects that give spool-shaped vertebrae. [15]. (Fig. 5, f). The bone in bone appearance in long bones and sandwich vertebral bodies are characteristic in osteopetrosis (Fig. 5, g) [10]. Spine Ap and lateral images confirms the clue radiographic findings in achondroplasia; short pedicles, progressive narrowing of interpeduncular distance, narrowed foramen magnum and posterior scalloping (Fig. 5, h).

Fig. 5 Spine:

a. Platyspondyly:  
spondyloepiphyseal dysplasia  
tarda



b. Abnormal segmentation:  
Spondylocostal dysostosis



c. Central beaking:  
Morquio's MPS IV



d. Anteroinferior Beaking,  
Hurler's MPS I



e. Coronal cleft spine:  
chondrodysplasia punctata



f. spool shaped vertebrae:  
Pyknodysostosis



g. sandwich vertebrae:  
osteopetrosis



h. Posterior scalloping and bullet shaped vertebrae achondroplasia



**Hand x-ray:** Hand x-ray can help in detecting many important diagnostic radiographical features, like the brachydactyly and trident shape in achondroplasia [7], preaxial (radial) polydactyly in Holt-Oram syndrome [16], or postaxial (ulnar) polydactyly in Ellis Van Creveld syndrome [17]. In MPS hand x-ray shows the short wide phalanges and fan-shaped base of metacarpals [18]. Acro-osteolysis with dense bones can confirm the diagnosis of pyknodysostosis [15]. The cone-shaped epiphysis is a sign of trichorhinophalangeal syndrome [19], (Fig. 6, a-f)

Fig. 6 Hand x-ray

a. Achondroplasia: trident hand, brachydactyly



b. Postaxial, ulnar, polydactyly  
Ellis Van Creveld Syndrome



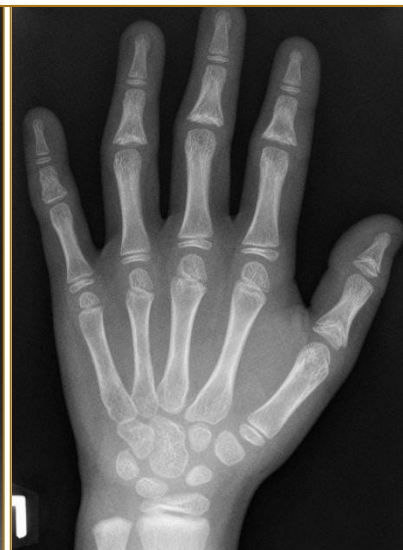
c. Preaxial, radial, polydactyly



d. MPS  
Fan-shaped MTC base  
short, wide phalanges



e. Trichorhinophalangeal syndrome  
cone-shaped epiphysis



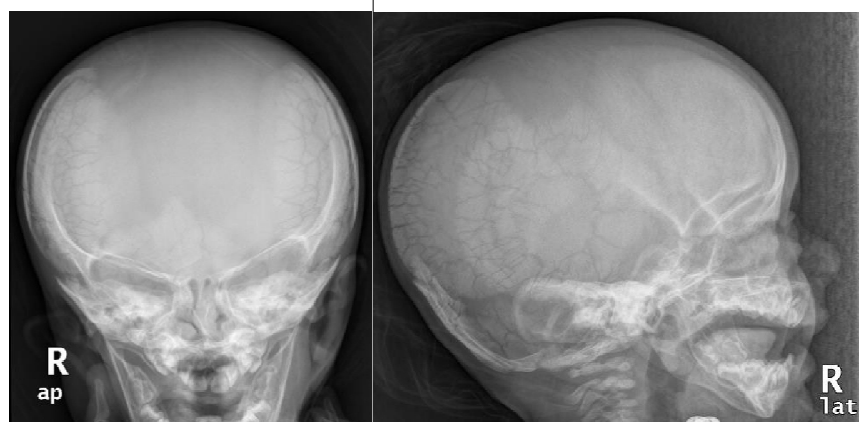
f. Pyknodysostosis  
Acroosteolysis



**Skull x-ray:** AP and lateral view in the skeletal survey shows many clue diagnostic signs. Wormian bones in lambdoid sutures in cleidocranial dysostosis [20], (Fig 7, a). Skull x-ray in pyknodysostosis show the typical obtuse mandibular angle, micrognathia, and other associated midface dysplastic features [15] (Fig. 7, b). Macrocephaly with bone sclerosis are signs in osteopathia striata with cranial sclerosis (OSCS). While the J-shape Sella turcica in lateral skull x-ray is an important clue finding in Hurler's syndrome MPS I [13], (Fig. 7, c). Enlarged calvaria, enlarged mandible, hypoplastic midface, frontal bossing, and narrow foramen magnum are signs of achondroplasia on skull x-ray [7,8,9], (Fig. 7, d).

Fig. 7 Skull:

a. Wormian bones Cleidocranial dysostosis



b. Pyknodysostosis: Obtuse mandible angle



c. J shaped Sella turcica:  
Hurler's disease MPS I



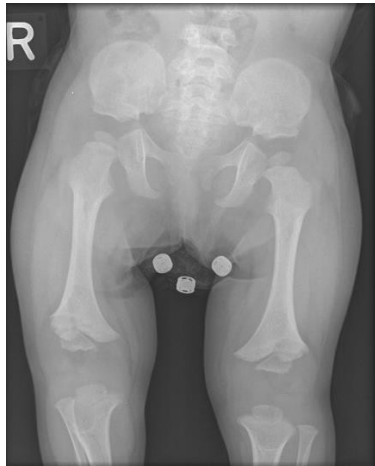
d. Achondroplasia: frontal bossing, large calvaria  
and mandible, small face, narrow foramen magnum



**Pelvis** AP view shows the characteristic "mickey mouse ear pelvis" in achondroplasia in which both iliac bones are flat and squared, with flat or horizontal acetabular angle and a pelvic inlet of champagne glass shape [21]. Wide pubic symphysis and wide sacroiliac joints are typical in cleidocranial dysostosis. The combination of iliac wings hypoplasia and femoral neck enlargement result in coxa vara [20]. In MPS, the acetabular fossa is shallow with a steep roof resulting in a sloping roof of the acetabulum [21]. While pelvis x-ray in mucopolipidosis type II shows the wide wings and narrow bodies of iliac bones, acetabula are hypoplastic [22,23]. (Fig. 8, a-d).

Fig. 8 Pelvis AP view

a. Achondroplasia



b. MPS



c. Cleidocranial dysostosis



d. Mucopolipidosis II



**Long bones:** Metaphyseal are wide with thinned overlying cortex that gives the typical Erlenmeyer-flask deformity in Pyle disease [11], (Fig. 3). Osteopetrosis will show the dense fragile bones that show the Erlenmeyer flask deformity and characteristic lucent metaphyseal bands [24], (Fig. 1, d). OI, the typical osteopenic bones with multiple fractures resulting in

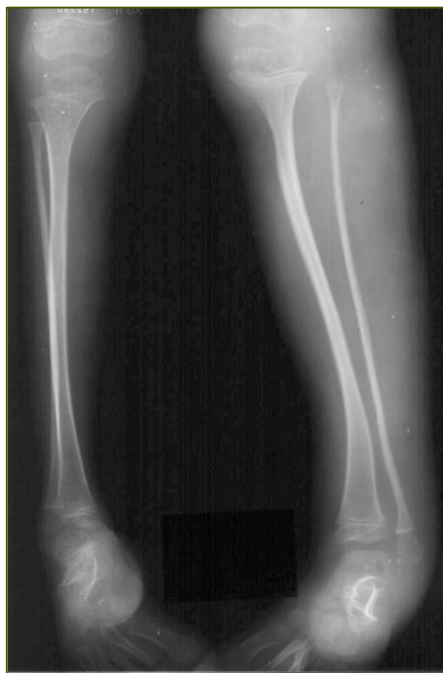
deformities [25], (Fig. 1, b). In achondroplasia, the tubular bones are short with a maintained diaphyseal diameter [7], (Fig. 1, a). Osteopathia striata x-ray shows the typical vertical metaphyseal and epiphyseal bands giving the appearance of a celery stalk [26], (Fig. 9, a). Mucopolidosis type II, femurs, and tibia may show rickets-like changes of metaphyseal fraying and widened along with the cloaking appearance and multiple fractures [22, 23], (Fig. 8, d). In neurofibromatosis 1 (Disorganized development of skeletal components group 29) the tibial pseudoarthrosis and gracile bones are typical [27], (Fig. 9, b). Extremities images in patients with osteogenesis imperfecta OI, will show multiple fractures and deformities. (Fig. 9, c).

Fig. 9: Long bones

a. Osteopathia striata



b. Neurofibromatosis I



### c. Osteogenesis Imperfecta OI



### Conclusion

Diagnosis of skeletal dysplasia is a teamwork not limited to clinicians, radiologists, and staff involved in the molecular and genetic assessment. Therefore, the systematic review of the skeletal survey combined with a detailed clinical assessment can help shorten the differential diagnosis list. Detecting the clue diagnostic signs related to each bone or body part with the constellation of other characteristic signs can help diagnose primarily. The frequently updated International Nomenclature of Constitutional Diseases of Bone is identifying more genes responsible for the above 400 disorders, thus helping clinicians and families have better plans and workup.

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