Overview of Skeletal Dysplasias

İskelet Displazilerine Genel Bakış

Tuğba DAŞAR[1], Esra KILIÇ[2]

[1]Department of Pediatric Genetics, Bilkent City Hospital, Ankara, Turkey
[2]Department of Pediatric Genetics, Bilkent City Hospital, University of Health Sciences, Ankara, Turkey

ABSTRACT

Skeletal dysplasias are quite a heterogeneous group of disorders, characterized by bone and cartilage abnormalities. Although each of them is individually rare, collectively the birth incidence is approximately 1 in 5000 live births. Due to the clinical heterogeneity, patients with skeletal dysplasias can apply to different departments with many different complaints or even lethal in the perinatal period. The establishment of a precise diagnosis provide proper clinical management of the patient, and a confirmed molecular diagnosis can prevent the recurrence of the disorder in the next generations. However, determining a spesific diagnosis is not always easy, yet a multisystemic, comprehensive, and stepwise approach to the patients with skeletal dysplasias, at least allows clinicians to classify into a specific group. In this review, general approach to patients with skeletal dysplasias, and some of the clinical and radiographic clues helpful in the diagnostic process are briefly summarized.

Key Words: Genetic disorders, Osteochondrodysplasias, Short stature, Skeletal dysplasias

ÖZ

İskelet displazileri kemik ve kıkırdak anormallikleri ile karakterize oldukça heterojen bir hastalık grubudur. Tek tek ele alındığında oldukça nadir olmakla birlikte bütüncül bakıldığında sıklığı yaklaşıl olarak 5000 doğumda 1'dir. Klinik heterojeniteye bağlı olarak hastalar farklı bölümlere farklı şikayetlerle başvurabilir ya da hastalar perinatal dönemde kaybedilebilir. Doğru tanı koymak, hastanın klinik takibinin uygun yapılmasını sağlar ve doğrulanmış moleküler tanı ile hastalığın sonraki nesillerde ortaya çıkmasının önüne geçilmiş olur. Ancak spesifik bir tanı koymak her zaman kolay değildir, ama multisistemik, kapsamlı ve basamaklı bir yaklaşım en azından spesifik bir grup içinde sınıflandırmayı sağlar. Bu yazıda iskelet displazili hastalara genel bir yaklaşım ve tanısal süreçte yardımcı olabilecek klinik ve radyolojik ipuçları kısaca özetlenmiştir.

Anahtar Kelimeler: Genetik hastalıklar, Osteokondrodisplazi, Boy kısalığı, İskelet displazisi

0000-0002-1493-4352 : DAŞAR T
0000-0003-0522-1809 : KILIÇ E

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Correspondence Address / Yazışma Adresi:

Tuğba DAŞAR
Department of Pediatric Genetics
Bilkent City Hospital, Ankara, Turkey
E-posta: tugbadasar@gmail.com

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INTRODUCTION

Skeletal dysplasias, also known as osteochondrodysplasias, are a large heterogeneous group of disorders, characterized by abnormal growth, differentiation, and development of bone and cartilage (1). Skeletal dysplasias are generally caused by variants in different genes, but they can also be related to extrinsic factors including maternal diseases and maternal drug use (2).

These disorders are individually rare, but the overall birth incidence is estimated to be about 2.4 to 4.5 per 10,000 live births, and represent %5 of all birth defects (2-4). Thanks to the advancements in the era of molecular genetics, and the development of genomic tools, many genes in the etiology of skeletal dysplasias have been delineated. It helps to understand the underlying pathophysiology and provides new therapeutic approaches. According to the Nosology of Genetic Skeletal Disorders, 2023 revision, genetic skeletal disorders encompass 771 entries resulting from variants in 552 known genes, and they are classified into 41 groups (Table I) (3). Due to clinical diversity, genetic heterogeneity, and individually rarity, recognizing them is not always easy (5,6). Obtaining a medical history, drawing a pedigree, physical examination, and assessment of radiographs in detail are essential in the evaluation of the patients with skeletal dysplasias.

CLINICAL EVALUATION

Skeletal dysplasias are quite a heterogeneous group of disorders, and patients with skeletal dysplasias can present with a wide variety of clinical findings. While some patients with skeletal dysplasia present with mild signs of osteoarthropathy starting in adolescence, some skeletal dysplasia can be lethal prenatally or life-limiting (2, 7-9). Even different variants in the same gene can cause quite different phenotypes. Loss of function variants in the FGFR3 gene cause CATSHL syndrome, a skeletal dysplasia with “tall stature”; while gain of function variants in the same gene cause Achondroplasia with “dwarfism”, Hypochondroplasia with “mild short stature” or Thanatophoric dysplasia that is usually “lethal” in the perinatal period (10).

To reach an accurate diagnosis or to narrow the differential diagnosis, a detailed clinical and radiographic evaluation is important, a stepwise aproach is essential (11, 12).

Medical history

Obtaining a detailed medical history of the patient is the first step in the assessment. The “onset of the symptoms” and “progression” should be asked. Medical history should include prenatal and natal history. Maternal illness, infections, and drug use during pregnancy should be noted. For example, maternal autoimmune disorders and exposure to warfarin prenatally cause chondrodysplasia punctata, and it is important to

Table I: Classification of skeletal dysplasias in the nosology of genetic skeletal disorders

Group 1	FGFR3 chondrodysplasias
Group 2	Type 2 collagen disorders
Group 3	Type 11 collagen disorders
Group 4	Sulfation disorders
Group 5	Dysplasias with multiple joint disloactions
Group 6	Filamins and related disorders
Group 7	Proteoglycan core protein disorders
Group 8	TRPV4 disorders
Group 9	Pseudoachondroplasia and multiple epiphyseal dysplasias
Group 10	Skeletal disorders caused by abnormalities of cilia or ciliary signaling
Group 11	Metaphyseal dysplasias
Group 12	Spondylometaphyseal dysplasias
Group 13	Spondyloepi(meta)physeal dysplasias
Group 14	Severe spondylodysplastic dysplasias
Group 15	Mesomelic and rhizo-mesomelic dysplasias
Group 16	Acromesomelic dysplasias
Group 17	Acromelic dysplasias
Group 18	Brachydactylies (isolated)
Group 19	Brachydactylies as part of syndromes
Group 20	Bent bone dysplasia group
Group 21	Primordial dwarfism and slender bones group
Group 22	Lysosomal storage diseases with skeletal involvement
Group 23	Chondrodysplasia punctata group
Group 24	Osteopetrosis and related osteoclast disorders
Group 25	Osteosclerotic disorders
Group 26	Osteogenesis imperfecta and bone fragility group
Group 27	Disorders of bone mineralisation
Group 28	Skeletal disorders of the parathyroid hormone signaling cascade
Group 29	Osteolysis group
Group 30	Disorganized development of skeletal components group
Group 31	Overgrowth (tall stature)syndromes and segmental overgrowth
Group 32	Genetic inflammatory or rheumatoid-like osteoarthropathies
Group 33	Cleidocranial dysplasia and related disorders
Group 34	Syndromes featuring craniosynostosis
Group 35	Craniofacial dysostoses
Group 36	Vertebral and costal dysostoses
Group 37	Patellar dysostoses
Group 38	Limb hypoplasia- reduction defects group
Group 39	Split hand/foot with or without other manifestations
Group 40	Polydactyly-syndactyly-triphalangism group
Group 41	Defects in joint formation and synostoses

Table II: Examples of clinical diagnostic clues in skeletal dysplasias

Physical examination	
Skull	Macrocephaly (Achondroplasia, Hypochondroplasia, Mucopolysaccahoridosis, Cole-Carpenter syndrome, Cranio-diaphyseal dysplasia, Cousin dysplasia) Cloverleaf skull (Tanatophoric dysplasia type 2) Large fontanelle (Osteogenesis imperfecta, Cleidocranial dysplasia, Opsismodysplasia) Triangular face (Kenny-Caffey syndrome)
Hair / Eyebrow	Sparse hair /eyebrow (Cartilage-hair hypoplasia) Alopecia (Chondrodysplasia punctata- Conradi Hunerman type) Light pigmentation of hair (AEC syndrome, EEC syndrome)
Eye	Blue sclera (Osteogenesis imperfecta) Wide palpebral fissures (Robinow syndrome) Hypertelorism (Robinow syndrome, Pfeiffer syndrome, Muenke syndrome, Saethre Chotzen syndrome) Otopalatodigital syndrome, Frank-Ter Haar syndrome, Lenz Majewski Hyperostotic dysplasia) Hypotelorism (Oculodentoosseous dysplasia) Microcornea (Oculodentoosseous dysplaia, Carpenter syndrome) Microphthalmia (Osteocraniostenosis, Kenny-Caffey syndrome) Proptosis (Thanatophoric dysplasia, craniosynostosis syndromes, Raine dysplasia) Blepharophimosis (Osteocraniostenosis, Schwartz Jampell syndrome) Buphthalmos (Melnick-Needles osteodysplasty) Lower eyelid coloboma (Nager syndrome) Ptosis (Baller-Gerold syndrome)
Nose	Depressed nasal bridge (Achondroplasia, Omodysplasia, Opsismodysplasia) Nasal bone hypoplasia (Keutel syndrome) Saddle nose (Sponastrime dysplasia) Pear-shaped nose (Tricho-rhino-phalangeal syndrome) Thin nose (Oculodentoosseous dysplasia) Hypoplastic ala nasi (Oculodentoosseous dysplasia) Parrot-like nose (Pyknodysostosis) Broad nose (Lenz-Majewski hyperostotic dysplasia) Thick bony wedge over glabella (Craniometaphyseal dysplasia) Prominent nose (MOPD) Midface hypoplasia (Achondroplasia, Stickler syndrome, craniosynostosis syndromes, Sponastrime dysplasia)
Chin	Rethrognathia (Stickler syndrome) Micrognathia (Cerebro-costo-mandibular syndrome) Prominent chin (Cartilage-hair hypoplasia) Prominent chin crease (Weaver syndrome)
Oral cavity	Cleft palate (Type 2 collagenopathies, Campomelic dysplasia, Catel-Manzke syndrome, Otopalatodigital syndrome) Multiple frenulum (Ellis-van Creveld syndrome) Alveolar ridge deformity (Robinow syndrome)
Teeth	Dentinogenesis imperfecta (Osteogenesis imperfecta, Odontochondrodysplasia) Supernumerary teeth (Cleidocranial dysplasia) Delayed eruption, enamel hypoplasia (Pycnodysostosis) Microdontia (Ellis van Creveld syndrome, Oculodentoosseous dysplasia, MOPD) Anodontia (AEC syndrome, EEC syndrome) Peg shaped teeth (Ellis van Creveld syndrome)
Ear	Cystic ear swelling (Diastrophic dysplasia) Petrified ears (Keutel dysplasia) Prominent ear crus (Saethre-Chotzen syndrome) Low-set ear (Roberts phocomelia syndrome, Baller-Gerold syndrome, Bent Bone dysplasia, Otopalatodigital syndrome, Spondylo-ocular dysplasia) Auditory canal atresia (SAMS syndrome)
Nail	Split nails (Condrodysplasia punctata- Conradi Hunerman type) Hypoplastic nails (Chondrodysplasia punctata- Brachytelephalangic type, Ellis-van Creveld dysplasia) Nail dysplasia (Nail-Patella syndrome, Yunis-Varon syndrome) Triangular lunula (Nail-Patella syndrome)
Spine	Cervical kyphosis (Larsen syndrome, Atelosteogenesis) Thoracolumbar kyphosis (Achondroplasia) Kyphoscoliosis (Osteogenesis imperfecta, Linkeropathy syndromes, Desbuquois dysplasia, Metatropic dysplasia) Increased lomber lordosis (Mucopolysaccharidosis, Achondroplasia) Short spine (SED congenita, Brachyolmia)

Physical examination	
Long bones	Bowing (Osteogenesis imperfecta, Stuve-Wiedeman syndrome, Campomelic dysplasia) Rhizomelic shortness (Achondroplasia, Hypochondroplasia, Boomerang dysplasia, Rhizomelic type Chondrodysplasia Punctata) Mesomelic shortness (Robinow syndrome, Leri Weill syndrome, Mesomelic dysplasia Langer type, AMDM) Rhizo-mesomelic dysplasia (Omodysplasia) Phocomelia (Roberts syndrome, Holt Oram syndrome, Tetra amelia syndrome)
Hands	Trident hand (Achondroplasia) Hitchikker thumb (Diastrophic dysplasia) Preaxial polydactyly (Townes Brock syndrome, Werner type mesomelic dysplasia) Postaxial polydactyly (Short rib polydactyly syndrome, Ellis van Creveld syndrome) Absent thumb (Yunis-Varon syndrome, Holt Oram syndrome, Duane Radial ray syndrome) Oligodactyly (Cornelia de Lange syndrome, Roberts syndrome, Fatco syndrome, Al Awadi syndrome) Syndactyly (Apert syndrome, Oculodentoosseous dysplasia, Werner type mesomelic dysplasia, Endosteal Hyperostosis Van Buchem type) Ectrodactyly (AEC syndrome, EEC syndrome) Cylindiric digits (Larsen syndrome) Crooked fingers (Tricho-rhino-phalangeal syndrome) Short hands (Geleophysic dysplasia, Acromicric dysplasia, Myhre dysplasia) Pudgy hands (Cartilage hair hypoplasia)
Feet	Club feet (Larsen syndrome, Diastrophic dysplasia, Achondrogenesis type 1B) Lateral deviation of fifth toe (IMPAD1 related dislocaiton syndrome) Short great toe (Fibrodysplasia ossificans proggressiva) Preaxial polydactyly (Carpenter syndrome)
Genital	Cryptorchidism (Robinow syndrome, Roberts syndrome, Al awadi syndrome) Ambiguous genitalia (Robinow syndrome, Campomelic dysplasia, Antley-Bixler syndrome, Short rib-polydactyly syndrome) Bifid scrotum (CDAGS) Hypospadias or micropenis (Robinow syndrome, IMAGE syndrome, Antley Bixler syndrome Cliteromegaly (Antley Bixler syndrome, Roberts syndrome) Large phallus (Roberts syndrome)
Skin	Achantosis nigricans (SADDAN dysplasia) Dimple at lower extremities (Campomelic dysplasia) Ichtiosiform erythrodermia (Chondrodysplasia punctata- Conradi Hunerman type) Erythroderma (EXTL3 deficiency) Thickened skin (Geleophysic dysplasia, Hyaline fibromatosis syndrome) Skin hyperextensiblity (B4GALT7 deficiency, B3GALT6 linkeropathy syndrome) Subcutaneous nodules (Hyaline fibromatosis syndrome, Winchester Torg syndrome) Skin rash- heterotopic ossification (Progressive osseous heteroplasia) Hypertrichosis/ hirshutism (Frank-Ter Haar syndrome, Diaphanospondylodysostosis syndrome, Bent bone dysplasia) Wrinkling of skin (Geroderma osteodysplasticum)
Systemic evaluation	
Cardiac system	ASD, VSD (Ellis-van Creveld syndrome, Holt Oram syndrome) Aortic root dilatation (B3GAT3-related linkeropathy syndrome) Thickening of heart valves (Geleophysic dysplasia)
Nervous system	Myotonia, contractures (Schwartz – Jampel syndrome) Decreased pain sensation, dysautonomia (Stüve-Wiedemann syndrome) Intellectual disability, developmental delay (Dyggvie-Melchior-Clausen dysplasia, Desbuquois dysplasia, Trichorhinophalangeal dysplasia type 2, NANS deficiency Microcephaly (MOPD)) Seizure (SADDAN)
Endocrine system	Hypocalcemia (Kenney-Caffey syndrome, Osteocraniostenosis, Albright hereditary osteodystrophy) Hypercalcemia (Hypophosphatasia, IMAGE syndrome, Metaphyseal chondrodysplasia Jansen type) Diabetes mellitus (Fibrous dysplasia (Mc-Cune Albright syndrome), MOPD, Wolcott-Rallison syndrome) Autoimmune tyhroiditis (SPENCD) Cushing disease, Hypertyhroidism (Fibrous dysplasia (Mc-Cune Albright syndrome)) Obesity (Carpenter syndrome, Albright's hereditary osteodystrophy) Adrenal insufficiency (IMAGE syndrome, Antley-Bixler syndrome)
Immunological system	Immune deficiency (Cartilage hair hypoplasia, EXTL3 deficiency, Schimke immuno-osseous dysplasia, SPENCD)

Systemic evaluation	
Renal system	Renal failure (Nail-Patella syndrome) Renal cysts (Asphyxiating thoracic dysplasia, Short-rib polydactyly syndromes) Nephrocalcinosis (Metaphyseal dysplasia- Jansen type)
Gastrointestinal system	Exocrine pancreatic insufficiency, pancreatic lipomatosis (Scwachman Diamond syndrome) Pancreatic cysts (Asphyxiating thoracic dysplasia, Short-rib polydactyly syndromes, Cranioectodermal dysplasia) Hepatosplenomegaly (Infantile osteopetrosis) Splenic hypoplasia/aspleni (Osteocraniostenosis) Liver fibrosis (Asphyxiating thoracic dysplasia)
Respiratory system	Laryngotracheomalacia (Campomelic dysplasia, Diastrophic Dysplasia, Atelosteogenesis type 3) Choanal stenosis/ atresia (Marshall Smith syndrome, Raine dysplasia, Lenz Majewski hyperostotic dysplasia)
Hematologic system	Cytopenia, anemia (Cartilage-Hair hypoplasia, Scwachman Diamond syndrome, Infantile osteopetrosis) Autoimmune hemolytic anemia (SPENCD)
Audiologic evaluaution	Hearing loss (Osteogenesis imperfecta, Type 2 collagenopathies, Stickler syndrome, Otopalatodigital syndrome, Myhre syndrome, Spondylo-ocular dysplasia, CATSHL syndrome)
Ophthalmological evaluaution	Miyopia, retinal detachment (Type 2 collagenopathies, Stickler syndrome) Hypermetropia (Kenny-Caffey syndrome, B4GALT7 deficiency) Cataract (Type 2 collagenopathies, Stickler syndrome, Spondylo-ocular dysplasia, osteocraniostenosis, Sponastrime dysplasia, CODAS syndrome, B4GALT7 deficiency, Chondrodysplasia punctata- Conradi Hunermann type and rhizomelic type) Microcornea (Oculodentoosseous dysplasia) Retinal pigmentary dystrophy (Mainzer-Saldino syndrome, Axial spondylometaphyseal dysplasia)
Ophthalmological evaluaution	Miyopia, retinal detachment (Type 2 collagenopathies, Stickler syndrome) Hypermetropia (Kenny-Caffey syndrome, B4GALT7 deficiency) Cataract (Type 2 collagenopathies, Stickler syndrome, Spondylo-ocular dysplasia, osteocraniostenosis, Sponastrime dysplasia, CODAS syndrome, B4GALT7 deficiency, Chondrodysplasia punctata- Conradi Hunermann type and rhizomelic type) Microcornea (Oculodentoosseous dysplasia) Retinal pigmentary dystrophy (Mainzer-Saldino syndrome, Axial spondylometaphyseal dysplasia)

question the mothers of the infants with stippling in this regard (10).

Short stature is one of the most common findings among patients with skeletal dysplasia, and it is important to know when it was noticed. For example, while the patients with 3M syndrome present with severe intrauterine growth restriction prenatally, and the birth length is approximately 40-42 cm; patients with pseudoachondroplasia are generally in normal length at birth, and short stature is detected at about 2 years (13). Patients with multiple epiphyseal dysplasia may not have short stature or height may be mildly shortened. These patients generally present with joint pain, waddling gait, and fatigue after long-distance walking in early childhood. Joint deformities and pain progress over time, and early-onset osteoarthritis requiring joint replacement can develop (14). PPRD (Progressive pseudorheumatoid dysplasia) is a skeletal dysplasia generally confused with Juvenile rheumatoid arthritis. Patients with PPRD are also normal at birth, and symptoms of arthropathy begin between three and six years with interphalangeal joint involvement. Large joints are also affected over time and progressive joint contractures develop (10). It is important to keep in mind skeletal dysplasias in patients presenting with joint pain.

Clinical findings may reverse over time, and the most typical example is Metatropic Dysplasia ("metatropos" means "changing pattern" in Greek) (15). While the patients with Metatropic Dysplasia have a short-limbed type of short stature at birth; in childhood, platyspondyly and kyphoscoliosis become more evident, and the trunk becomes shorter than the limbs (short-trunked short stature) (15).

Severe developmental delay and intellectual disability are not common among patients with skeletal dysplasia, but these patients may have delays at motor milestones due to discrepancies in body parts, bone deformities, or joint laxity (9). Neuromotor milestones should be noted. Only a few skeletal dysplasia including Dyggve-Melchior-Clausen dysplasia and NANS deficiency may have severe developmental delay and cognitive impairment (10). Patients should be asked about recurrent fractures or dislocations, time of teeth eruption, hearing loss, ophthalmologic problems, and diseases related to other systems. When evaluating a patient with short-limbed short stature, noticing the sparse-thin hair and eyebrows, and knowing the accompanying immune deficiency and cytopenia will be very helpful in the diagnosis of Cartilage hair hypoplasia.

Some of the diagnostic clinical clues in skeletal dysplasias are shown in Table II.

Family history

A detailed family history is essential, and it should be asked whether there are similar family members. Other affected patients in the family may help for the diagnosis. Height of the

parents should be noted and parents should be evaluated for skeletal deformities.

Physical examination

After obtaining a detailed medical and family history, a comprehensive physical examination may give many clues to determine the clinical diagnosis. Evaluation of facial dysmorphic features, head shape, joint, chest, spine, long bone, hand, and feet deformities should be noted. Clinical findings that can help to narrow the differential diagnosis are summarized in Table II. Anthropometric measurements should include head circumference, height, weight, arm span, and upper /lower segment ratio (6,12). Armspan and upper/lower segment ratio are important to determine whether the short stature is proportionate or disproportionate. Armspan is the distance between the tips of the middle fingers when the patient is standing upright against the wall (16). Although the arm span/ height ratio varies depending on age, gender, and ethnicity, it is approximately 1, and there should not be more than a 5 cm difference between height and arm span (7). The lower segment is the distance between the floor and the top of the symphysis pubis. The upper segment is calculated by subtracting the lower segment from the height. Age-related curves of the arm span- height difference and US/LS ratio are used for ethnicity and each sex. The normal upper/lower segment (US/LS) ratio is about 1.7 in newborns and decreases with age. At about 10 years old upper and lower segment lengths are equalized (7). Spondyloepiphyseal dysplasia congenital and Brachyolmia are examples of short-trunked skeletal dysplasias (10).

If the limbs are involved, segments of the extremities should be measured to detect which segment is primarily affected (upper segments (femur and humerus): rhizomelic; middle segments (radius, ulna, tibia, and fibula): mesomelic; and distal segments (hands and feet): acromelic). Achondroplasia, the most common skeletal dysplasia, is an example of rhizomelic short stature (17). Patients with Robinow syndrome, characterized by fetal face appearence, genital anomalies and costovertebral segmentation defects, exhibit mesomelic brachymelia (10). Geleophysic dysplasia is one of the acromelic dysplasias, characterized by happy-natured appearence, joint contractures and short hands and feet (10).

Radiologic evaluation

The majority of skeletal dysplasias have a distinguishable pattern of skeletal changes, and radiological evaluation of skeletal dysplasias depends on pattern recognition (18). A systematic stepwise radiographic approach can provide a specific diagnosis with the clinical details (1,18, 19). To determine which parts of the skeleton are mainly affected, a comprehensive skeletal survey including anteroposterior (AP) and lateral view of the skull, spine, and foot, AP view of thorax, pelvis, left hand and wrist, unilateral tubular bone graphies is needed (6, 12, 19). In case of limb asymmetry or suspicion of epiphyseal stippling, both upper and lower limb graphies should be obtained (20).

If the patient has previous graphies, they should be evaluated since the radiographic findings may change over time. In Chondrodysplasia punctata, epiphyseal stippling can not be seen after age two or three (10). In Pseudoachondroplasia, the finding of “anterior beaking” in vertebrae in early life changes to platyspondyly over time (10). Moreover, recognition of many skeletal dysplasias becomes challenging after epiphyseal fusion, and in adults, it is very important to obtain prepubertal skeletal graphies. In patients with multiple epiphyseal dysplasias, degenerative joint disease is progressive and results in early-onset osteoarthritis (14). In these patients, it is not easy to make a diagnosis of multiple epiphyseal dysplasia either in adults since epiphyses are fused, or in infants before epiphysis appear (14). Repeating the skeletal survey later in undiagnosed patients may be helpful (20).

Assessment of the radiographies includes evaluation of bone age, mineralization, structure, size, shape, and epiphyseal - metaphyseal – diaphyseal ossification (20). Some of the radiographic clues for skeletal dysplasias are shown in Table III.

Bone Age

Although there are various methods to determination the bone maturation, the most widely used one is hand and wrist radiograph of the non-dominant hand. Bone age is generally normal in patients with skeletal dysplasia, but can be delayed in epiphyseal dysplasias or advanced in Larsen syndrome or Desbuquois syndrome (9, 10).

Mineralization

Imbalance between bone formation and bone resorption causes osteopenia or osteosclerosis resulting with recurrent fractures. Osteogenesis imperfecta is a heterogeneous group of disorders characterized by decreased bone density, and it is the most common form of hereditary bone fragility disorder (22). Clinical severity is quite variable, and it may be lethal in perinatal period. Hypophosphatasia is another example of hypomineralization, and in severe lethal form, bones may be almost completely unossified (boneless fetus) (1,23). Metaphyseal lucencies and mid-diaphyseal spurs (Bowdler spurs) are other characteristic features of Hypophosphatasia (23). Osteosclerosis, increased bone formation, may be generalized (Osteopetrosis, Pyknodysostosis); may appear as bone islands (Osteopoikilosis) or metaphyseal striations (Sponastrime dysplasia, Osteopathia striata) (10). As well, graphies should also be evaluated for heterotopic calcifications in soft tissues, as in the Fibrodysplasia ossificans progressiva (10).

Calvarium

General ossification, shape and thickness of the skull, sizes of fontanelles, presence of wormian bones should be evaluated (24). In Achondroplasia an enlarged skull vault, frontal bossing,

Table III: Examples of radiographic diagnostic clues in skeletal dysplasias

Skull	Wormian bones (Osteogenesis imperfecta, Hajdu Cheney syndrome, Cleidocranial dysplasia) Thick skull (Myhre syndrome, Mucopolysaccahoridosis) Copper-beaten appearence (Hypophosphatasia, Cole-Carpenter syndrome) J sella (Geleophysic dysplasia, Mucopolysaccahoridosis) Obtuse mandibular angle (Pyknodysostosis) Intracranial calcification (Dysosteosclerosis, Osteopetrosis with renal calcification, Raine dysplasia)
Vertebrae	Decreased interpedicular distance in lumbar vertebrae (Achondroplasia) Dorsal hump (SED Tarda) Double hump (Dyggvie-Melchior-Clausen syndrome) Coronal clefts (SED congenita, Kniest dysplasia) Diamond-shaped vertebra (Pseudoachondroplasia) Pear shaped vertebra (SED congenita) Anisospondyly (Dissegmental dysplasia) Absent thoracic vertebral pedicles (Campomelic dysplasia) Cobra sign spine (Achondrogenesis type 1B) Sandwich appearence -sclerotic endplates- (Osteopetrosis) Codfish vertebra (Osteogenesis imperfecta, Cole Carpenter syndrome) Irregular endplates (Brachyolmia, Mucolipidosis type 3…) Overfaced pedicle (Metatropic dysplasia) Segmentation defects (Spondylocostal dysostosis)
Scapulae	Hypoplastic scapula (Campomelic dysplasia) Plump scapula (Mucopolysaccharidosis) Small misshapen scapula (Achondrogenesis) Hypoplastic scapula (Campomelic dysplasia, Cousin dysplasia, Cleidocranial dysplasia)
Ribs	Thick ribs (Mucopolysaccharidosis) Thin ribs (3M syndrome) Unossified rib gaps (Cerebro-costo-mandibular syndrome) Posterior rib gaps (Ischiospinal dysostosis) Ribbon-like ribs (Melnick Needle syndrome) Short ribs (SRPS, ATD) Wavy ribs (Bent bone dysplasia) Coat hanger ribs (Cranioectodermal dysplasia)
Clavicles	Hypoplastic/aplastic clavicle (Cleidocranial dysplasia) Thick clavicles (Mucopolysaccharidosis) Mustache-shaped small clavicles (Bent Bone dysplasia) Ram-horn bowing of the clavicles (SADDAN dysplasia) Handle-bar clavicle (Ellis van Creveld dysplasia, ATD, SRPD)
Pelvis	Square shape iliac bones (Achondroplasia) Small iliac wings (Achondrogenesis, Campomelic dysplasia, Cleidocranial dysplasia) Absent pubic ossification (SED congenita, Achondrogenesis, Hypochondrogenesis) Widely spaced pubic bones (Cleidocranial dysplasia) Trident pelvis (Achondroplasia, Tanataphoric dysplasia, Short-rib polydactyly syndromes) Champagne glass (Achondroplasia) Iliac horns (Nail-patella syndrome) Snail-like pelvis (Scneckenbecken dysplasia) Lacy appearance of iliac crests (Dygvie-Melchior-Clausen syndrome, Smith McCort syndrome) Hypoplasia of ischial rami (Ischio-pubic-patellar dysplasia) Unossified ischial rami (Ischiospinal dysostosis) Wide ischiopubic syndchondrosis (Cleidocranial dysplasia)
Long bones	Madelung deformity (Leri Weil dysostosis) Absent Radius (TAR syndrome, Holt Oram syndrome) Radio-ulnar synostosis (Nager syndrome, linkeropathy syndromes, Humeroradial synostosis (Cousin dysplasia) Hypoplasia of distal humeri (Diastrophic dysplasia, Larsen syndrome) Bifid distal humeri (CHST3 related dislocation syndrome) Ovoid lucency of proximal femur (Achondroplasia) Swedish key / Monkey wrench appearance (Desbuquois syndrome) Chevron deformity (Achondroplasia) Dumbell shape (Metatropic dysplasia, Kniest dysplasia, Fibrochondrogenesis Periost reaction (Hyaline fibromatosis syndrome)

Long bones	Gracile bones (3M syndrome, Osteocraniostenosis) Bowing (Osteogenesis imperfecta, Hypophosphatasia, Campomelic dysplasia, Thanatophoric dysplasia type 1, Melnick Needle syndrome) Accordion like tubular bones (Osteogenesis imperfecta type 2) Popcorn-like calcification (Osteogenesi imperfecta type 3) Ossification of the forearm interosseous membrane (Osteogenesi imperfecta type 5) Dripping candle wax (Melorrheostosis) Fibular aplasia (Nager syndrome)
Hands / Feet	Advanced bone age (Larsen syndrome, Desbuquois dysplasia) Delayed bone age (Multiple epiphyseal dysplasia) Bifid thumb (Desbuquois dysplasia, Robinow syndrome, Holt Oram syndrome) Bullet-shaped phalanges (Mucopolysaccharidosis) Cone shaped epiphysis (Cartilage-hair hypoplasia) Bifid distal phalanx of the thumb (Larsen syndrome) Proximal metacarpal pointing (Mucopolysaccharidosis) Ball in socket appearence (Pseudoachondroplasia) Acroosteolysis (Pyknodysostosis, Hajdu Cheney syndrome, Mandibuloacral dysplasia) Angel-shaped phalanges (ASPED dysplasia, Bent bone dysplasia, Spondylo megaepi-metaphyseal dysplasia) Chevron-shaped epiphysis (Acrodysostosis) Multiple ossification centers in calcaneus (Larsen syndrome) Supernumerary carpal and tarsal bone ossification centers (Larsen syndrome) Macroepiphysis (Spondylomegaepiphyseal metaphyseal dysplasia, OSMED)
Patella	Patellar hypoplasia (Nail-patella syndrome, Meier-Gorlin syndrome, Genitopatellar syndrome, Ischiopatellar dysplasia) Double-layered patella (SLC26A2-related multiple epiphyseal dysplasia)

*****For abbreviations: Bone Dysplasia, 4th edition*

midface hypoplasia and short skull base are observed. In Frontometaphyseal dysplasia, torus-like overgrowth of the supraorbital ridges and sclerosis of the skull base are typical (10). Large fontanelle and delay in its closure are seen in Osteogenesis imperfecta, Hypophosphatasia, Cleidocranial dysplasia, Pyknodysostosis (10). Premature fusion of cranial sutures result with abnormal skull shape (brachycephaly, dolichocephaly, plagyocephaly, turricephaly, trigonocephaly). Thanatophoric dysplasia type 2 is associated with cloverleaf skull. Turribrachycephaly is seen in Cole-Carpenter syndrome (10). Wormian bones are abnormal new bones developing from extra ossification centers, and they are located within the lambdoid or coronal sutures generally. Up to ten wormian bones are consider as normal variant, but more than ten wormian bones are seen in many conditions including Osteogenesis imperfecta, Cleidocranial dysplasia, Pyknodysostosis, Hajdu Cheney syndrome (24). Craniovertebral junction anomalies may cause significant morbidities and mortality in skeletal dysplasias such as foramen magnum stenosis in Achondroplasia or atlanto-axial instability due to odontoid hypoplasia in SED congenita (24, 25). So it is important to evaluate the skull graphies carefully.

Chest

Assesment of clavicles, ribs and scapula may give significant clues in the diagnosis of skeletal dysplasias. For example, the finding of hypoplastic scapula is very helpful in diagnosing Campomelic dysplasia. Absence or hypoplasia of clavicles with small and deformed scapulae is a clue for Cleidocranial dysplasia.

Rib assessment includes assesment of ossification, number, length, thickness, shape, fractures or fusion. Rib fusion with vertebra segmentation defects is typical for Spondylocostal dysostosis (crab-like chest). Paddle-shaped ribs are observed in mucopolysaccharidosis, wavy ribs are seen in Melnick Needle syndrome (26). Beaded ribs are a feature of Achondrogenesis type 1A and osteogenesis imperfecta type 2A. In Asphyxiating thoracic dysplasia, formerly known as Jeune syndrome, ribs are short, and the narrow thorax result with respiratory problems (10).

Spine

Dorsolumbar spine radiographs are essential part of the skeletal survey (27). In spine assessment, general shape of vertebral bodies (anisospondyly, platyspondyly, square / foreshortened / ovoid vertebra, hemivertebra, irregular enplates), posterior scalloping, ossification defects, stippling, notching, coronal or sagital clefts, pedicles, interpedicular distance, presence of kyphoscoliosis, increased or decreased lordosis should be evaluated.

Platyspondyly means flattened vertebra and can be seen in many skeletal dysplasias. In Thanatophoric dysplasia, vertebral bodies are strikingly flat (wafer-thin vertebral bodies) and in a H-shaped configuration. In Osteogenesis imperfecta codfish vertebrae (biconcave appearance of vertebrae) may be seen. In Achondrogenesis, vertebral body ossification is poor, but pedicle ossification is preserved (27). In osteopetrosis, sclerotic endplates give a sandwich-like appearence. The interpedicular distance expands caudally, but patients with Achondroplasia do not exhibit interpedicular widening.

Pelvis

Pelvis is constituted by pubic, iliac, ischial bones and sacrum (28). Detailed assesment of pelvic bones may provide many clues for skeletal dysplasia.

Ilium: Ilium should be assessed for shape (flared, square, hypoplastic, foreshortened, tombstone-like, crescent-shaped, halberd-shaped, snail-like appearance notching, lacy crest, iliac horns, champagne glass appearence…), osteopenia or sclerosis (bone-in-bone appearance, sunburst appearance, sclerotic oval focuses). Acetabular roofs may be flat, horizontal, sloping, irregular, or trident-shaped.

Pubis: Thickness and ossification of the pubis should be noted. Absent or retarded pubic ossification is an important finding in the diagnosis of SED congenita, achondrogenesis, and hypochondrogenesis.

Ischium: Thickness, tilt, and ossification of ischial bones should be assessed. Detecting an ischial anomaly can narrow the differential diagnosis (Ischiospinal dysostosis, Ischio-patellar syndrome).

Long Tubular Bones

Tubular bone assessment includes length, shape, mineralization, epiphysis, metaphysis, diaphysis, presence of bowing, exostoses, and enchondromas. In short-limbed skeletal dysplasias, it is important to determine which segment is more prominently affected to classify the skeletal dysplasia. It should be noted that the radiological evaluation of the segmental shortness of the long tubular bones (rhizomelic/ mesomelic/ acromelic) is more correct than clinical visualization (21). Achondroplasia, the most common skeletal dysplasia, is an example of rhizomelic shortness.

Likewise, determining the involvement of the epiphysis, metaphysis or diaphysis is also very important for classification. These regions can be affected isolated or in different combinations, and grouped according to the affected regions (Multiple epiphyseal dysplasias, metaphyseal dysplasias, spondyloepiphyseal dysplasias, spondylometaphyseal dysplasias, spondyloepimetaphyseal dysplasias). In multiple epiphyseal dysplasia, before the clinical symptoms appear, delayed ossification of the epiphysis is observed. Later epiphyses appear small and flat with irregular contours (14). Metaphyseal irregularities in metaphyseal dysplasias include flaring, splaying and cupping. Cartilage hair hypoplasia is an example of metaphyseal dysplasia, and knee metaphyses are most prominently affected (29). Camurati Engelman disease is a progressive diaphyseal dysplasia and characterized by hyperostosis primarily affecting the long bones and skull (10). Endosteal and periosteal proliferation, cortical thickening and patcy sclerosis are observed in diaphyses (10).

Hands and Feet

In hand graphies, overall morphology, length, shape, number of bones, mineralization, epiphysis, metaphysis, and diaphysis of the tubular bones, joint configuration, and presence of brachydactyly, syndactyly, oligodactyly, polydactyly (preaxial/ mesoaxial/ postaxial), ectrodactyly, symphalangism, pseudo epiphysis, carpal and tarsal bone fusions, stippling, osteolysis, exostoses, and Madelung deformity are evaluated (30). In a patient with spine malsegmentation, detecting carpo-tarsal coalition may be very helpful in diagnosing Spondylocarpotarsal synostosis syndrome. Cone-shaped epiphysis with metatarsal shortening in a patient with sparse hair, eyebrow and pear-shaped nose is helpful for Tricho-rhino-phalangeal syndrome. In Mucopolysaccharidoses, trabeculation is coarsely laced, tubular bones of the hands are short, wide, and deformed, proximal and middle phalanges are in bullet shape, second to fifth metacarpal bones are tapered proximally (10). Foot graphies are also evaluated similarly.

GENETIC EVALUATION

The last part in the assessment is genetic evaluation. With the advances in the field of genetics, many genes in the etiology of disorders including skeletal dysplasias have been identified. Due to clinical overlapping and heterogeneity, it is not easy to recognize a specific skeletal dysplasia type, with the clinical and radiographic findings. One of the most common skeletal dysplasia, Osteogenesis imperfecta, is caused by 21 known genes so far, the most common being COL1A1 and COL1A2 (22). While some of the subtypes of osteogenesis imperfecta are inherited autosomal dominantly, some of them are inherited autosomal recessively or X-linked recessively. Making a clinical diagnosis of Osteogenesis imperfecta without genetic tests, can not provide enough information for the family about the risk of recurrence. So it is important to have a confirmed molecular diagnosis, even if the clinical diagnosis is certain.

Different variants in the same gene may cause different disorders, and the typical example is the COL2A1 gene. In the OMIM database, 15 different entities related to COL2A1, with clinical findings ranging from mild osteoarthrosis to lethal achondrogenesis, have been reported (25).

If the patients have a specific clinical diagnosis, sanger sequencing and MLPA analysis of the relevant gene may be performed, but due to clinical and genetic heterogeneity, and rarity of the disorders, in many centers skeletal dysplasia gene panels or whole exome sequencing and microarray analysis (for suspected copy number variants) are being performed. In some centers, optical genome mapping and whole genome sequencing are performed, and they increase the diagnostic yield. Analysis of the genetic tests should be performed by specialist experienced in this field. A genetically confirmed diagnosis provide an improved clinical care for the patient, and genetic counseling to the family to prevent the disorder in the next generations (31).

MANAGEMENT

Management of the skeletal dysplasias is generally symptomatic and supportive, and still largely rehabilitation and surgical intervention. Patients should be assessed regularly in a multisystemic way. In skeletal dysplasias affecting spine, clinicians should be careful about spine compression and should perform neurologic assessment for myelopathy, regularly. To assess the instability of the occipito-cervical junction, flexion-extension cervical films are necessary (32). Patients with a high risk of airway obstruction (mucopolysaccharidosis, achondroplasia) should undergo polysomnography. Severe kyphoscoliosis cause respiratory failure and requires regular respiratory function tests. In Geleophysic dysplasia, progressive cardiac valvular disease is observed, and echocardiography is important in the follow-up (10). Eye examination is important in patients with SED congenita, as miyopia, retinal detachment, and cataract may develop over time (10). An accurate diagnosis in patients with skeletal dysplasia ensures appropriate medical follow-up.

The development of genomic technology enabled to understanding the pathophysiology of the disorders, and allowed new approaches such as pharmacological theraphy, cellular theraphy, or gene therapy (31). In Hypophosphatasia and Morquio A, enzyme replacement therapy (asfotase alfa and elosulfase alfa, respectively), in Osteogenesis imperfecta biphosphonates and in Achondroplasia vosorotide (CNP analog, BMN111) treatments are used currently, and many new treatment options in Achondroplasia, Osteogenesis imperfecta, osteopetrosis, Fibrodysplasia ossificans progressiva and hereditary multiple exostosis are about to complete phase 2 and 3 studies (4,31). In the near future, it is hoped to be used personalized gene theraphy and cell therapy safely and widely (33).

CONCLUSION

Skeletal dysplasias are clinically, genetically, and radiologically quite heterogeneous disorders. A multisystemic and comprehensive approach (detailed medical and family history, pedigree, physical examination, appropriate radiographs and genetic tests) is required. An accurate diagnosis is essential for the management of the patient, genetic counseling, and future treatment options in skeletal dysplasias.

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